RESEARCH COMMUNICATION

Skin Phenotype and the Impact of Surveillance on Melanoma in New Zealand

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Abstract

Few studies have been performed to evaluate the effect of skin surveillance on melanoma risk. This population-based case-control study was carried out to confirm the association of phenotype with melanoma and to investigate the effect of surveillance by skin examination on the risk of melanoma in New Zealand. Cases were patients with a first diagnosis of in-situ or invasive cutaneous malignant melanoma from three regions of New Zealand. Controls were selected at random from the electoral rolls and frequency-matched by age. Participants included men and women of European origin aged between 20 and 79 years. A strong association was found between host phenotypic factors (red hair, fair skin, many freckles on the face, and numbers of moles) and melanoma risk. These effects were largely independent of each other.The relative risk of melanoma was significantly reduced after skin examination by one's self, partner or a health professional; this reduction in risk remained after adjustment for phenotype, mole counts, skin reaction to sun, and exposure to sun. People who attended a 'skin check clinic' had a non-significant increase in risk of melanoma.

Key words: melanoma - skin surveillance – phenotype - screening

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Introduction

The incidence rate of malignant melanoma has shown a large increase in New Zealand over the past 30 years (Cooke et al. 1983; Cooke and McNoe 1990). New Zealand and Australia now have the highest melanoma incidence rates in the world (MacLennan et al. 1992; Armstrong and Kricker 1994). Analysis of recent trends indicates that the melanoma burden will continue to increase in New Zealand, with the projected rate of deaths from melanoma being 8.8 per 100,000 men and 3.5 per 100,000 women in the years 2002–2006 (Cox 1995). In New Zealand, as in other countries, melanoma is mainly a disease of the Caucasian population: the age-standardised incidence of melanoma in New Zealand in non-Maori is about ten times higher than in Maori (30.9 per 100,000 and 2.9 per 100,000 respectively, in 1996) (New Zealand Health Information Service 2000).

Exposure to sunlight is the only known risk factor for melanoma that can be altered (Elwood and Gallagher 1994). However, individuals who are exposed to sunlight are not equally susceptible to melanoma, differences which result primarily from host factor variation (Holly et al. 1995). Acquired moles are the strongest indicators of melanoma risk and there is now good evidence that they, too, may be induced by sunlight (MacKie et al., 1997; Østerlind, 1997; Sancho-Garnier et al., 1997).

There is compelling intuitive appeal that the early detection of melanoma will be rewarding but the evidence of actual benefit from skin surveillance is limited (Koh et al. 1989). Unlike in other countries (Koh et al. 1995), there are no organized population screening programmes for melanoma in New Zealand, but skin surveillance (either by a health professional, a friend or oneself), plus "skin check days" are being encouraged by public education campaigns. These campaigns also seek to increase awareness of malignant melanoma generally by providing information on how melanoma could be prevented or detected earlier.

The case-control study described here is the first population-based study of "screening" by skin surveillance for melanoma in New Zealand, a country in which approximately 80% of the 3.6 million inhabitants have fair-skinned European ancestors (Statistics New Zealand 1998). The study was carried out to confirm the association between phenotype and the risk of melanoma and to evaluate the effect of skin examination on melanoma risk.

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Methods

All histopathology reports for patients aged 20 to 79 years with a first diagnosis of in-situ or invasive cutaneous malignant melanoma or Hutchinson's melanotic freckle (lentigo maligna) were collected prospectively over two years, from 1 July 1992 until 31 June 1994, from three regions of New Zealand (Hawkes Bay, Bay of Plenty and Nelson-Marlborough). Duplicate reports, recurrences, re-excisions and second and subsequent melanomas arising in the same patient were excluded. The pathology reports came from both public and private laboratories in these regions and the criteria for the diagnosis of melanoma and Hutchinson's melanotic freckle were those used by pathologists in their normal diagnostic practice. Dysplastic moles were excluded.

An almost complete listing (95% complete) of New Zealand residents 18 years and over is available on the electoral roll. Controls were selected at random from the current electoral roll and frequency-matched by age in 10 year groups to be intermediate between the age distribution of the general population and the age distribution of the melanoma cases.

Each general practitioner and consultant was written to for permission to approach their patient for an interview. We then sought consent from the patient in writing. Cases were interviewed between three months and one year of their initial diagnosis. This procedure was approved by the regional ethics committees.

Data

Data were collected by trained interviewers using a standard telephone interview of approximately 30 minutes. For a widely dispersed population such as New Zealand this is accepted as the best method to obtain a maximum response rate and collect high quality information (Paul et al. 1986). The questionnaire was designed to collect information from participants about basic demographic characteristics, experience of skin surveillance, family history of melanoma, medical history including other skin cancers, phenotypic variables such as skin colour, eye colour, hair colour, and mole numbers, acute and chronic skin reaction to sunlight and sunburn, history of sun exposure including occupational and recreational exposure before and after the age of 18 years, and in addition for patients with melanoma, presenting symptoms and diagnostic histories. This questionnaire included validated questions used in case-control studies in Canada (Gallagher et al. 1986) and the United Kingdom (Elwood et al. 1990) supplemented with pictures of skin pigmentation from Perth, Australia (personal communication from Dallas English, 1992).

Approximately a week before interview, participants were sent an information pack including photographs of moles to aid identification, a measurement card for measuring their moles, and 'moleyness' and 'freckling' indicators. For the moleyness indicator, subjects chose from a series of diagrams (none, few, moderate or many moles), the one which most closely represented the number of moles on their body. The freckling indicator comprised six diagrams of faces with different densities of freckling, ranging from 'no freckling' to 'covered in freckles'. Participants chose which diagram most closely represented their facial freckling. Because there were very few people with the highest levels of freckling, the top three categories were combined into one – many freckles. In addition, participants were asked to count the moles (≥ 2mm and ≥ 5mm in diameter) on their right arm and the number of moles ≥ 5mm diameter on their entire body before the interview. The reliability of self-reported mole counts has been verified in previous work in Australia (Dubin et al. 1986).

The study was restricted to people of predominantly European origin. At the beginning of each interview, participants were asked which ethnic group they identified with, and their skin colouring. All Europeans and others without dark skin completed the interview.

The main occupations of men were coded according to the New Zealand Standard Classification of Occupations, 1987 (Statistics New Zealand 1987). Retired men were asked for their main occupation while in paid employment. Women who gave their occupation as housewife were asked to provide their husband's or partner's occupation. Socioeconomic status was categorised from a high of 1 to a low of 6, according to occupation using the Elley-Irving scale (Elley and Irving 1985). Education was categorised by self-reported highest level of education reached, from primary school to University or Polytechnic degrees and diplomas.

Hair colour was self-reported in one of seven categories: black, dark brown or brunette, light brown, fair or blond, red or auburn, grey, or white. Noone reported grey or white hair as a teenager. Eye colour was self-reported as brown, hazel, green, grey or blue. Skin colour was self-reported as one of four categories: dark, olive/Mediterranean, medium or fair. There was no direct observation of participants by interviewers.

Several different measures of skin surveillance were used; a casual self-examination of the skin in the two years before diagnosis (or two years before interview for controls), a deliberate and purposeful self-examination of the skin in the previous two years, a deliberate and purposeful self-examination of the skin in the previous five years, a deliberate and purposeful skin examination by a partner in the previous two or five years, a skin examination by a health professional in the previous two or five years, or attendance at a skin check clinic. The intensity of skin screening was estimated by collecting information on the frequency of self-screening and partner skin examinations in the two years before diagnosis or interview.

Data analysis

Disease exposure associations were described by calculating odds ratios and their 95% confidence intervals. For univariate analyses the odds ratios and 95% confidence limits were calculated in SPSS-X from 2 x 2 tables (Mantel

and Haenszel 1959). Confidence intervals were estimated by the procedure of Cornfield (1956) as programmed by Thomas (1975).

Odds ratios were adjusted for age in 5-year groups, region and sex. Multiple logistic regression was used with ordered categorical independent variables (Breslow and Day 1980) using the computer programme SPSS-X. To minimize the number of factors to be included in the final model in addition to age, sex and region, the three most important phenotypic factors were amalgamated into a phenotype risk score. The three variables, teenage hair colour (5 categories), skin colour (dark/olive, medium, or fair) and freckling (6 categories) were ranked in order of risk, their category numbers added, and then the resultant risk scores (from low risk 3 to high risk 14) grouped into approximate tertiles. This categorical variable (phenotype risk score) was then used to adjust for confounding by phenotype. Inclusion in the final model of four variables; ever/never sunburnt with blisters, sunburns before the age of 20, occupational activities mainly indoor or outdoor before the age of 18, and occupational activities mainly indoor or outdoor after 18 years, were found to best adjust for confounding by sun exposure and skin reaction to sun. Tests for trend were calculated using the method of Breslow and Day (1980).

When invasive and in-situ melanomas were considered separately there was little difference in the associations with measures of skin surveillance. Therefore, to maximize the power of these analyses all melanomas, in-situ and invasive, were combined.

Results

Five hundred and fifteen people were enrolled as potentially eligible subjects for the case-control study. We wrote to the physicians of these patients and received consent to approach 483 of them. Of these patients, consent and interviews were obtained from 415. Thirty-eight participants were ineligible for inclusion because they had a previous diagnosis of melanoma and seven interviews were abandoned because of deafness or memory loss, leaving 370 for analysis.

Of 573 people selected as controls from the electoral rolls who were mailed a request to participate, 7 were found to be ineligible before contact was made (one was a dark-skinned Maori, four had died, and two had no phone), consent was received from 304, refusal from 207 and no contact could be made with 55. Of the controls who gave consent, 31 were found to be ineligible (two had no phone, one was too deaf, six had moved out of the area or overseas, three had a previous melanoma and 19 were non-Europeans with dark skin). Twenty seven of those who refused were also found to be ineligible (one had no phone, five were too deaf, six had moved overseas, two were non-Europeans with dark skin, six were mentally impaired, and seven were too ill). Of the 453 suitable participants (304 consents + 207 refusals – 58 ineligibles) with whom contact could be made, 61% participated. A total of 277 control interviews were completed of which 271 were suitable for final inclusion.

Because the age distribution for controls was designed to be intermediate between the age distribution for cases and the age distribution of the general population, controls were, on average, younger than cases. Approximately 5% of cases and 15% of controls were aged from 20 to 29 years, and 20% of cases and 16% of controls were aged from 70 to 79 years. The sex distribution for cases and controls was very similar with about 50% male participants. Slightly more cases were in the higher social classes and had higher levels of education than controls but these differences were not significant (p=0.77 and 0.73 respectively). Fewer cases than controls were single (p for heterogeneity in marital status =0.02).

The risks of melanoma (invasive and in-situ combined) associated with phenotypic characteristics are shown in Table 1. Having red hair as a teenager, fair skin and freckling on the face were associated with an increased risk of melanoma. After adjustment for the other phenotypic variables, each remained a significant independent risk factor (data not shown).

The risk of melanoma was positively associated with moles for all self-reported measures of mole counts (Table 2), with odds ratios for the highest categories ranging from 2.7 to 9.4. For each of these measures there was a significant positive trend ($p<0.001$) in increasing risk of melanoma with increasing numbers of moles. After adjustment of each mole variable for phenotype risk score, factors related to sun exposure and skin reaction to sun, all mole variables remained as significant risk factors for melanoma. Subjects who reported other family members having large moles had about double the risk of melanoma compared to those with no family history of large moles (Table 2).

For all measures of skin surveillance (except attendance at a skin check clinic) the adjusted odds ratios of 0.2 to 0.4 were significantly below one (Table 3), implying a significant reduction in risk of melanoma from skin examination by one's self, partner or health professional. Further adjustment by education, social class and marital status made no difference to the odds ratio estimates; nor did adjustment for skin reaction to sun and sun exposure.

If skin examinations identify melanomas earlier in their natural history than would otherwise occur, it is expected that the depth of lesions at diagnosis would be different in people who examine their skin compared with those who do not. However, the median depth of melanomas was similar irrespective of whether or not the patient had performed deliberate skin self-examinations in the previous two years (0.71mm and 0.80mm, respectively).

For each category of melanoma depth (in-situ, and invasive <0.76, 0.76-1.5, >1.5mm), skin examination by one's self, one's partner or by a health professional showed a protective effect (OR between 0.2 to 0.7) with most associations being statistically significant (data not shown). Attendance at a skin clinic was not significantly associated with melanoma of any depth category.

All measures of the intensity of skin surveillance (ever/

Table 1. Phenotypic Factors and Risk of Melanoma (In-situ and Invasive Combined).

	Cases n=369	Controls n=271	Adjusted[a]OR (95% CI)	
Hair colour as teenager:				
black / dark brown	112	101	1.0	
light brown / fair	211	155	1.3 (0.9 – 1.9)	
red	47	14	3.9 (1.9 – 7.7)	
Eye colour:				
brown	60	42	1.0	
hazel	61	59	0.7 (0.4 – 1.2)	
green	59	37	1.1 (0.6 - 2.0)	
grey/blue	190	133	1.0 (0.6 - 1.6)	
Skin colour:				
dark / olive	25	35	1.0	
medium	117	109	1.7 (0.9 - 3.2)	
fair	228	127	2.7 (1.5 - 4.8)	[b]p for trend< 0.001
Facial freckling:				
none	198	170	1.0	
few	105	76	1.6 (1.1 - 2.4)	
moderate	26	16	2.2 (1.1 – 4.6)	
many	41	9	5.9 (2.6 – 13.3)	p for trend <0.001

[a]adjusted for sex, age in 5-year groups, and region
[b]p for trend is across ordered categories

Table 2. Mole Counts and Risk of Melanoma (Invasive and In-situ Combined).

	cases n=370	controls n=271	Adjusted[a] OR (95% CI)	Phenotype & sun adjusted[b] OR (95% CI)
≥2mm moles on right arm				
0	135	114	1.0	1.0
1-3	81	70	1.2 (0.8 - 1.8)	1.3 (0.8 - 2.1)
4-10	84	54	1.6 (1.0 - 2.5)	1.7 (1.0 - 2.7)
11+	70	32	2.7 (1.6 - 4.6)	3.0 (1.7 - 5.4)
			[c]p for trend<0.001	p for trend<0.001
≥5mm moles on right arm				
0	205	186	1.0	1.0
1	61	43	1.3 (0.9 - 2.1)	1.3 (0.8 - 2.2)
2-3	60	35	1.6 (1.0 - 2.6)	1.6 (1.0 - 2.6)
4+	43	6	6.5 (2.7 – 15.9)	5.9 (2.3 -14.8)
			p for trend <0.001	p for trend<0.001
Total body large (>5mm) moles				
0	62	86	1.0	1.0
1-2	79	66	1.6 (1.0 - 2.6)	1.8 (1.1 - 3.0)
3-5	78	50	2.3 (1.4 - 3.8)	2.4 (1.4 - 4.1)
6-10	57	33	2.5 (1.4 - 4.4)	2.8 (1.5 - 5.1)
11+	92	35	3.8 (2.2 - 6.5)	3.8 (2.1 - 6.6)
			p for trend <0.001	p for trend<0.001
Moleyness indicator				
none	51	50	1.0	1.0
few	183	162	1.2 (0.8 - 2.0)	1.2 (0.7 - 2.0)
mod	100	54	2.2 (1.3 – 3.9)	2.2 (1.2 - 4.0)
many	36	5	9.4 (3.2 - 27.3)	8.0 (2.7 - 23.9)
			p for trend <0.001	p for trend<0.001
Large (>5mm) moles in family member				
no	110	109	1	1.0
yes	184	101	2.1 (1.4 - 3.2)	1.9 (1.3 - 3.0)

[a] adjusted for sex, age in 5-year groups and region
[b] each variable also adjusted for phenotype risk score, skin reaction to sun and sun exposure
[c] p for trend is across ordered categories

Table 3. Skin Surveillance and Risk of Melanoma (In-situ and Invasive Combined).

	Cases (n)	Controls (n)	Adjusted[a] OR (95% CI)		Phenotype and sun adjusted[b] OR (95% CI)	
Casual self skin check, during previous 2 years:						
no	167	51	1.0		1.0	
yes	196	220	0.3	(0.2 - 0.4)	0.2	(0.1 - 0.3)
Deliberate self skin check, during previous 2 years:						
no	288	169	1.0		1.0	
yes	81	102	0.5	(0.3 - 0.7)	0.4	(0.3 - 0.6)
Deliberate skin check, during previous 5 years:						
no	282	157	1.0		1.0	
yes	87	113	0.4	(0.3 - 0.6)	0.3	(0.2 - 0.5)
Deliberate partner skin check, during previous 2 years:						
no	253	158	1.0		1.0	
yes	58	68	0.5	(0.3 - 0.8)	0.4	(0.2 - 0.6)
Deliberate partner skin check, during previous 5 years:						
no	252	152	1.0		1.0	
yes	59	73	0.5	(0.3 - 0.7)	0.3	(0.2 - 0.5)
Doctor skin check exam, during previous 2 years:						
no	292	187	1.0		1.0	
yes	78	84	0.5	(0.4 - 0.8)	0.5	(0.3 - 0.7)
Doctor skin check exam, during previous 5 years:						
no	271	162	1.0		1.0	
yes	98	109	0.5	(0.3 - 0.7)	0.4	(0.3 - 0.6)
Attend skin check clinic:						
no	319	242	1.0		1.0	
yes	51	29	1.3	(0.8 - 2.2)	1.2	(0.7 - 2.2)

[a] adjusted for sex, age in 5-year groups and region

[b] each variable also adjusted for phenotype risk score, large mole count, skin reaction to sun and sun exposure

never deliberate self skin check in previous 2 years, deliberate self skin check <12 times per year or 12+ times per year, ever/never skin check by partner in previous years, skin check by partner 1-2 times, 3-6 times or 6+ times in previous 2 years) significantly reduced the risk of melanoma (OR from 0.3 to 0.5).

Discussion

This population-based case-control study in New Zealand has confirmed the associations of phenotypic factors including the presence of moles, with the risk of melanoma and has shown a protective effect of most measures of skin surveillance.

Phenotypic characteristics, such as hair colour, eye colour, skin colour and freckling, have been assessed in a variety of ways, from self-reporting to comparison with standardized colour charts, and the effects of phenotype on melanoma risk have been reasonably consistent in all these studies (Østerlind et al. 1988; MacKie et al. 1989; Elwood et al. 1990; Marrett et al. 1992; Holly et al. 1995). The current investigation found an increased risk of melanoma with red hair as a teenager, fair skin and many freckles in accord with previous studies, but no effect of eye colour on melanoma risk.

Moles are common in light-skinned populations and there is now good evidence that they, as well as melanomas, may be induced by sunlight (MacKie et al. 1997; Østerlind 1997; Sancho-Garnier et al. 1997). Moles appear first in childhood, reach a maximum in early adulthood and progressively decrease in number with age (Cooke et al. 1985; MacKie et al. 1985). As in most studies (MacKie et al. 1989; Elwood

et al. 1990; Carli et al. 1995; Holly et al. 1995; Grulich 1996) we have found an increasing risk with increasing numbers of moles, irrespective of the definition of mole used.

We found a significantly reduced risk of in-situ and invasive melanoma in subjects who underwent any type of skin screening examination (except attendance at a skin check clinic), whether performed by themselves, a health professional or their partner. A similar protective effect of skin self-examination was also obtained by the only other case-control study of screening and melanoma (Berwick et al. 1996) which assessed the risk of lethal melanoma. These two studies were carried out on two different populations (USA and New Zealand) with differing underlying rates of melanoma but the results are similar both in terms of the direction of the screening effect and its magnitude.

The association of skin surveillance with a reduced incidence of melanoma has analogies with reductions in tumour incidence at other sites. Rates of cervical cancer reduced significantly after the introduction of cervical screening and the removal of precancerous lesions (WHO 1986). Screening which results in a decreased incidence of melanoma can only directly occur as a result of the removal of precancerous lesions. Alternatively it is possible that precursors with a higher malignant potential may be more often removed in people who perform skin examinations. However, in this study, although patients with melanoma had more skin lesions removed, there was no significant difference in the self-reported numbers of skin lesions removed in people who carried out skin examinations compared with those who did not.

Skin surveillance may diagnose melanomas that would have remained clinically benign and never diagnosed (Burton and Armstrong 1994), resulting in an apparent increase in incidence of total melanoma and a relative over-diagnosis of superficial lesions. Early lesions identified by "screening" may progress more slowly and have a different natural history to those diagnosed because of symptoms. However, neither in this study nor that by Berwick et al (1996), was there a higher risk of melanoma among those who examined their skin more frequently.

Elwood (1996) has suggested that skin self-examination should produce a shift towards thinner lesions and show the maximal protective effect for deep melanomas. Although in the current study it was not possible to distinguish screen detected lesions from the others, the protective effect from skin surveillance was seen for deep as well as thin and in-situ melanomas.

The present study suggests a tendency towards an increase in risk of melanoma associated with attendance at 'skin check clinics'. From other evidence (McGee et al. 1994) it appears that these clinics act as diagnostic clinics for in-situ or thin invasive melanoma, rather than 'screening clinics'. In the current study, although three melanomas were diagnosed at skin clinics, 43% of attenders went specifically to have a suspicious "spot" examined and another 10 (13%) attended because they were at higher risk of developing melanoma. It is possible that people who examine their skin regularly are also likely to stay out of the sun or have fewer risk factors for melanoma. However, in the present study the odds ratios found for skin surveillance remained significantly less than unity when adjusted for phenotype, mole numbers and our measures of sun exposure.

The collection of data about skin examinations in Berwick's study (Berwick et al. 1996) and this one relied on recall by participants and were not able to be verified. With publicity about the importance of early diagnosis of melanomas and New Zealand campaigns to encourage the examination of one's skin, it is possible that patients with melanoma and controls without the disease would remember and report their experience of skin examinations differently. If patients with melanoma under-report their skin surveillance practices, and controls over-report, this would result in an overestimate of the protective effects of surveillance.

There is potential for selection bias in the controls in this study as their consent rate was not high - about 61% of those who could be contacted. Although this rate was lower than anticipated, it is reasonably similar to the response rates in Western Canada (between 48% and 59% of eligible controls were interviewed) (Elwood et al. 1985), and in Australia where 69% of eligible controls were interviewed (Holman et al. 1986). Controls may not have been representative of the general population in that they may have been more likely to engage in health protection behaviours. Lead-time bias is unlikely to have had a large impact on this study as participants who performed skin examinations did not have significantly thinner, less invasive melanomas than those who did not examine their skin, and the protective effect from screening was not maximal for thick melanomas. It would be of value to follow-up these patients after 10 years to investigate whether skin surveillance confers a protection against progression to advanced or lethal melanoma.

In summary, this study confirms the association of phenotype with melanoma risk found in most other studies. The results relating to skin surveillance and melanoma risk are in agreement with the protective effect seen in the only other published case-control study of "screening" in the USA. Thus this protective effect has been observed in two different populations with different underlying rates both of melanoma and its risk factors.

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