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Public awareness about risk factors could pose problems for case-control studies: The example of sunbed use and cutaneous melanoma

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Abstract

In a large case-control study we found no association between sunbed use and melanoma risk, but indications for potential recall and recruitment biases made the interpretation of the results difficult. Associations with skin phototype (adj OR for skin type I *vs.* IV: (2.6, 95% CI 1.5–4.8)), hair colour (adj OR red/blond *vs.* brown/black 2.0 (95% CI 1.4–2.8)) and number of naevi on both arms (OR $>$ 10 *vs.* $\leqslant$10 3.13 (95% CI: 2.47; 3.97)) were comparable to previous studies, but negative associations were found between sun exposure and melanoma risk (adj. OR 0.87 (95% CI: 0.65–1.18)) and in cases between sun exposure and naevus count. These observations led us to speculate that cases may have underreported their sun exposure and, most likely, their sunbed exposure. High percentages of sunbed use among controls indicated possible recruitment bias: eligible controls who were sunbed users were probably more likely to accept the invitation to participate than non-users, possibly due to a feeling of 'guilt' or 'worry' about their habits. Such selective participation may have strongly influenced the risk estimates of sunbed use in our study.

Keywords: Bias; Case-control study; Melanoma; Sunbed

Case-control studies have several advantages over other types of analytical epidemiological studies, especially when studying a relatively rare disease: they can generally be performed in a much shorter time period than cohort studies; do not require such a large sample size as cohort studies and are therefore cheaper. Despite their usefulness and wide applicability, case-control studies have limitations and biases might occur [1,2]. First, in case-control studies the information on risk factors is collected from cases after their diagnosis and this might pose serious biases in self-reported past exposures. It is generally thought that greater effort on the part of cases to remember past exposures, knowledge about risk factors for the disease, or tendency for changes in behaviour following diagnosis or treatment

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influence the accuracy of reporting among cases (''recall bias''). This can lead to what is referred to as ''differential misclassification'' and, finally, to biased estimates of risk. Second, participation rates in case-control studies are frequently low and often lower in controls than cases. Bias can arise because the reasons why cases and controls choose (or refuse) to take part in a study may be related to exposures of interest. In general, biases can occur in case-control studies of all types of disease but they are more likely to occur when there has been a great deal of public information about the relation between potential or established risk factors and the disease. This is particularly relevant for melanoma because people are more and more aware of the hazards associated with sun exposure. Using a case-control study of melanoma in twins and asking melanoma cases and their co-twins to quantify their own exposures and asking both twins which twin had the greater exposure, researchers found evidence of bias in reports of sunbathing in childhood and adulthood and possibly of freckling in childhood, with cases tending to overestimate their sun exposure [3]. More evidence that case-control status influences reporting of risk factors came from a study conducted in the cohort of the Nurse's Health Study. The ability to tan reported by women diagnosed of melanoma was lower than that reported by the same women before the diagnosis [4].

We present here the problems encountered in a case-control study assessing the association between sunbed exposure and melanoma risk in Europe. In order to study the effects of sunbeds on melanoma risk, one must correct for important confounders, such as skin type and exposure to natural sunlight, as well as protective measures (such as wearing protective clothing, hats, staying out of the sun and using sunscreens) taken before the diagnosis. We described the problems encountered in this study and the implications it might have for studying known risk factors in a well-informed population. The case-control study was performed in Sweden, the Netherlands, the United Kingdom, Belgium and France, collecting data from 597 melanoma cases and 622 controls eligible for analysis, aged between 18 and 50 years. Trained interviewers interviewed both cases and controls and performed a naevus count on both arms. The recruitment of cases was through hospitals or population based cancer registries. Controls were either randomly selected from population registries, selected from lists of patients attending GP practices, selected through door-to-door searches or recruited through an advertisement in a local newspaper. In the Netherlands the local ethics committee requested that participants be informed about the purpose of the study, including giving information about the risks of sun exposure for melanoma. During the interview, using a standardised questionnaire, respondents were asked about sunbathing habits and sunbed use. Demographic data as well as data on skin type, eye and hair colour and freckles were also collected. The questions about sunbed use over a lifetime were aided by showing two coloured charts with 12 pictures of sunbed and sunlamp devices commonly used in Europe since the 1950s. Details of the study are described in Bataille and colleagues, published in this issue [5].

We observed large differences in prevalence of sunbed use in both cases and controls in the various participating countries, with considerable, though non significant, differences in the odds ratio (OR) estimates per country (Table 1).

With increasing prevalence of sunbed use (when comparing countries), an apparent trend was observed with decreasing ORs but this did not reach significance. The overall adjusted odds ratio for melanoma with ever *vs.* never sunbed use was smaller than one (adjusted OR 0.85 95% CI (0.64; 1.13)) (Table 1). In our study, ever sunbed use in controls varied from 19% in France up to 86% in Sweden. This high prevalence of sunbed use in controls in our study (Table 1) was compared to those in other recent case-control studies: 59% of controls used sunbeds in Sweden [6] and 26% in the United Kingdom [7] although these studies included older cases and controls which may have created lower prevalence of sunbed use as sunbed use significantly decreases with age. In countries where many health campaigns for skin cancers have been organised and melanoma incidence is high (Sweden, Netherlands, England), the knowledge of the normal population regarding potential melanoma risk factors, including sunbeds, is likely to be high [2].

Before adjusting for sun exposure, we investigated the association between reported sun exposure and melanoma risk. We observed a negative association between sun exposure and melanoma risk. The adjusted OR for ever *vs.* never sunbathing and melanoma was 0.87 (95% CI: 0.65–1.18) (Table 2). This is not in agreement with published data: in a meta-analysis of 20 case-control studies on intermittent sun exposure and melanoma risk the summary OR for intermittent sun exposure was 1.87 (95% CI 1.67–2.09) [8]. However, the associations with reported skin phototype (adj OR for skin type I *vs.* skin type IV: 2.6, 95% CI 1.5–4.8) and interviewer-determined hair colour (adj OR red or blond *vs.* brown/black 2.0 (95% CI 1.4–2.8)) was confirmed in our study (Table 2).

Numerous epidemiological studies in similar Caucasian populations have found that sunbathing activities increase the risk of melanoma, especially in case of intermittent exposures and in younger age groups [8–10]. The apparent ''protective'' effect on melanoma associated with sunbathing in our study raised the hypothesis that to some extent, our findings could be attributable to the underreporting of sunbathing by melanoma cases.

In this study, numbers of naevi on the arms were also measured, by trained interviewers. The number of naevi counted on both arms were higher for melanoma cases

Table 1
Sunbed use after the age of 15 years and risk of melanoma

Country	Sunbed use >14 yr	Cases ($n = 597$)		Controls ($N = 622$)		Crude OR	95% CI	Adj. OR[a]	95% CI
		n	%	*n*	%				
Sweden	No	18	20	12	13	1		1	
	Yes	71	80	79	87	0.60	(0.27–1.33)	0.62	(0.24–1.64)
Netherlands	No	40	27	35	21	1		1	
	Yes	106	73	132	79	0.70	(0.42–1.18)	0.90	(0.46–1.76)
United Kingdom	No	79	52	74	46	1		1	
	Yes	74	48	87	54	0.79	(0.51–1.24)	0.96	(0.55–1.67)
Belgium	No	14	33	15	37	1		1	
	Yes	28	67	25	63	1.2	(0.48–2.97)	1.50	(0.40–5.63)
France	No	131	78	132	81	1		1	
	Yes	36	22	31	19	1.17	(0.68–2.00)	1.03	(0.51–2.11)
All countries	No	282	47	268	43	1		1	
	Yes	315	53	354	57	0.86	(0.69–1.08)	0.85	(0.64–1.13)

[a] Adjusted for age, sex, haircolour, phototype, number of sunburns before and after 15 years of age, number of holiday weeks in sunny areas.

Table 2
Sun exposure and sun protection habits in cases and controls and melanoma risk

		Cases $n = 597$	Controls $n = 622$	Adj. OR[a]	95% CI	Other studies (reference)
Age	Mean (SD)	38 (7.8)	37 (7.8)	1.01	(0.99; 1.03)	
Sex	Female	378	408	1.00		
Hair colour	Brown/black	122	184	1.00		
	Light brown	283	324	1.16	(0.81; 1.66)	
	Blond/red	191	115	1.97	(1.36; 2.84)	
	Male	219	214	1.07	(0.79; 1.46)	
Skin type	IV (good tanner)	61	118	1.00		
	III	194	273	1.38	(0.85; 2.24)	
	II	245	171	2.11	(1.27; 3.51)	
	I (never tan)	97	60	2.64	(1.46; 4.78)	
Sunburn < age 15	No	308	375	1.00		
	Yes	289	247	1.11	(0.80; 1.50)	
Sunburn ⩾ age 15	No	174	230	1.00		
	Yes	423	392	1.15	(0.84; 1.57)	
Annual nr. of holiday weeks in sunny areas	⩽1.5	157	161	1.00		
	1.5–3	200	202	1.03	(0.72; 1.47)	⩾1 wk: 1.44 (0.89–2.34) [9]
	⩾3	240	259	0.96	(0.68; 1.35)	
Sunbathing aged ⩾15[b]	No	233	189	1.00		
	Yes	364	433	0.87	(0.65; 1.18)	1.87 (1.67–2.09) [8][c]

[a] Adjusted for age, sex, haircolour, phototype, number of sunburns before and after 15 years of age.
[b] Reference category: Never sunbathe after the age of 15.
[c] In this study [8], a summary OR for sun exposure was given based on 20 studies.

(median = 18, interquartile range: 6–37) than for controls (median = 7.5, interquartile range: 2.5–17). The odds ratio for having more than 10 naevi on both arms compared to having 10 or less naevi was 3.13 (95% CI: 2.47;3.97). There was a (non-significant) variation between countries: the median number of naevi on arms for controls was 10 for the United Kingdom, 7 for the Netherlands and Sweden, 6 for France and 5 for Belgium.

Naevus counts have been positively correlated with high levels of sun exposure in many Caucasian populations [11–16]. We therefore checked this established association between sun exposure and naevus count separately in our cases and controls. The positive association between sun exposure before the age of 15 and naevus count was confirmed in controls in our study for reported episodes of sunburn during childhood (Table 3). For reported sunburns in cases both before 15 and after the age of 14, and for reported sunburns in controls after the age of 14, the association was weaker and not significantly increased. However, reported sunbathing in adulthood appeared inversely related to naevus counts in cases, albeit not significantly. The more the reported sunbathing took place during the warmest hours of the day, the stronger the negative association with naevus count. This negative association was stronger in cases than controls. However, it is possible that increased sun

Table 3
Percentage change in naevi count on arms for cases and controls according to sunburns and sun exposure in a European case-control study

		Cases		Controls	
		% Change[a]	95% CI	% Change[a]	95% CI
Sunburns before 15 years of age	Never	Ref.		Ref.	
	Ever	4.5	(−3.4; 11.2)	9.9	(3.1; 15.8)
Sunburns 15 years and older	Never	Ref.		Ref.	
	Ever	1.5	(−8.0; 9.3)	2.8	(−6.1; 10.1)
Number of holiday weeks per year	0–1	Ref.		Ref.	
	2	1.7	(−9.4; 10.5)	10.4	(1.4; 17.8)
	3 or more	−1.9	(−13.7; 7.4)	3.0	(−7.8 ; 11.6)
Sunbathing	Never	Ref.		Ref.	
	Ever	−7.8	(−18.7; 0.9)	0.3	(−0.9; 8.1)

[a] Percent change in the number of naevi issued from a Poisson regression with a scale parameter for overdispersion, adjusted for country, age, sex, haircolour, sunburns before and after 15 years old.

exposure, which leads to the expression of solar elastosis and solar lentigines, makes the naevi disappear faster in adulthood. This may in part explain why those who have higher sun exposure have lower naevus counts. The negative association between signs of sun damage such as solar elastosis and solar keratoses and naevus counts in adulthood has been reported by others [15,17].

A substudy was performed in the Netherlands [18] assessing case's knowledge about melanoma risk factors. The results showed that 56% of the melanoma cases did not believe that their melanoma had anything to do with sun exposure and it is therefore possible that they underreported their true exposure. This is despite the information provided on sun exposure and melanoma in the information sheet given to the participants before the interview as well as the regular media campaigns on melanoma and sun exposure in the Netherlands.

These observations led us to hypothesise that certain cases may have denied that they could have been 'responsible' for their melanomas and therefore underreported their intentional sun exposure, and, most likely, their sunbed exposure as well.

Eligible controls who used sunbeds were probably more likely to accept the invitation to participate in a melanoma study than those who did not use sunbeds, as was reflected in the very high percentage of sunbed users amongst controls (Table 1); this may have created a selection bias. This selective participation amongst controls who were sunbed users might be due to a feeling of 'guilt' or 'worry' about their habits or an idea that they may be more 'useful' for the study because they were sunbed users. The inclusion of controls who were more likely to use sunbeds would therefore dilute the true risk of sunbed use in melanoma.

Our results suggest that both melanoma cases and controls in this study underreported their sun exposure, but this was more severe in cases. Our data is also possibly affected by the need to provide 'socially desirable answers' amongst cases and controls, but especially amongst cases. A reason for their underreporting may be a 'search for explanations that are beyond their control', thereby avoiding blaming themselves for their serious disease. This is in line with earlier studies performed amongst patients of serious illnesses [18,19].

Whilst we cannot rule out the possibility that sunbed use is not a risk factor for melanoma and may even be protective, the indications for potential biases in recruitment and recall make it impossible to rely on risk estimates derived from our analyses. The data presented here highlight the need to be aware of potential recall and selection biases when studying an exposure for a disease in a well educated and informed population.

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