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Left-sided excess of invasive cutaneous melanoma in six countries

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ABSTRACT

To investigate the laterality of cutaneous melanoma (ICD-10 C43), we obtained data spanning the period of diagnosis 1998–2003 from six population-based cancer registries: New South Wales, Australia; England; Finland; The Netherlands; Scotland; and the Surveillance Epidemiology and End Results (SEER) Program of the United States of America (restricted to 'White' race category only). For cases with laterality recorded, the overall ratios of left- to right-sided tumours were calculated. We found that left to right ratios were consistently greater than 1.00, ranging from 1.08 (New South Wales, Australia and US SEER 'White') to 1.18 (Scotland), with an overall ratio for all registries combined of 1.10 (95% confidence interval 1.08–1.11). There were no statistically significant differences by sex or age group for all sub-sites combined, or for upper limb or lower limb melanomas. The excess of left-sided tumours seems unlikely to be explained by chance or recording bias. The most likely explanations would appear to be either differences in sun exposure and/or asymmetry of melanocyte distribution or characteristics arising at the time of embryological development.

1. Introduction

In a recent UK study, the epidemiological correlates of cancer laterality in five major paired organs were examined.[1] The authors found asymmetries in cancer incidence coinciding with differences in organ size and, for selected sites, differences in survival according to tumour laterality. The search for explanations for such observations could potentially lead to a greater understanding of the aetiology of cancer.

Cutaneous melanoma is a tumour that has increased in incidence rapidly across the world, with striking differences in incidence between countries.[2] Despite the possibility of asymmetrical exposure to solar radiation resulting, for example, from drivers exposing one arm through open vehicle windows, as far as we can establish, there have been no stud-

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ies of the laterality of cutaneous melanoma reported in the literature. In the present study, we explored the laterality of cutaneous melanoma in six countries, our null hypothesis being that these tumours are distributed symmetrically on either side of the midline.

2. Materials and methods

Aggregated cancer registration data on the laterality of invasive cutaneous melanoma (ICD-10 C43) diagnosed during the period 1998–2003 were obtained for the following populations: New South Wales in Australia; England; Finland; The Netherlands; Scotland; and US Surveillance Epidemiology and End Results (SEER) 'White'.[3] The laterality variable is recorded in slightly different ways by different cancer registries. As well as left and right, the other potential options in use by some registries include bilateral, central, unilateral but side unspecified, not applicable, not a paired site, not known, not recorded, and blank. In practice, as far as cutaneous melanoma is concerned, the majority of other options recorded fall into the last five categories. The number (%) of cases allocated codes other than for left or right by registry were as follows: New South Wales in Australia 5412 (30%); England 18,684 (49%); Finland 2211 (55%); The Netherlands 3514 (22%); Scotland 1215 (28%) and US SEER 'White' 12,083 (20%).

For cases with laterality recorded, the overall ratios of left- to right-sided tumours were calculated, and exact 95% confidence intervals for the ratios were generated under the assumption that the number of left-sided tumours followed a binomial distribution. The χ^2 test for association was used to assess differences in laterality by age group (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and $\geqslant$80 years), and by sex. Data were analysed for all tumour sites combined, and for tumours of the upper limb (ICD-10 C43.6) and lower limb (C43.7) separately.

3. Results

The total numbers of left-sided and right-sided melanomas were 51,338 and 46,883, respectively (Table 1). The left to right ratios were consistently greater than 1.00, ranging from 1.08 (New South Wales, Australia and US SEER 'White') to 1.18 (Scotland), with an overall ratio of 1.10 (95% confidence intervals 1.08–1.11). There were no statistically significant differences by sex or age group for all sub-sites combined, nor for upper limb or lower limb melanomas separately (Table 2). The excess of left-sided tumours was generally consistent across cancer registries, anatomical sub-sites, age groups, and between the sexes (data not shown, but available on request).

4. Discussion

The results of our study indicate a small but generally consistent excess of left-sided cutaneous melanomas. There are several potential reasons why a left to right excess might arise.

Firstly, the observation may simply reflect the play of chance. This is very unlikely because a similar excess of left-sided tumours is found in all of the cancer registries studied.

Secondly, there is a possibility of recording bias. Recording bias could arise if those responsible for collecting cancer registration data were confused about the codes for left and right. However, this seems to be an unlikely explanation because a recent study of laterality at different major tumour sites found that most apart from breast had a *deficit* of left-sided tumours.[1] Furthermore, the laterality codes contained in the Finnish data were meticulously assigned, specifically for this study, based on the free text description of the exact location of the primary tumour site that is stored in the Finnish Cancer Registry database.

Thirdly, the left-sided excess may reflect differences in exposure to sunlight, arising through a number of potential mechanisms. Differences might occur in relation to right- or left-handedness, with around 11.5% of the general population being left-handed.[4] While handedness might result in differential application of sunscreen to the arms, this argument is unlikely to apply to the legs or to young children (who have sunscreen applied by their parents). The fact that there is an excess of left-sided melanomas on the lower as well as the upper limb makes handedness a less convincing explanation. The left-sided excess on the lower limb, and the fact that most vehicles in the United Kingdom are driven from the right side, also makes it unlikely that the left-sided excess could be explained by drivers exposing their left arms through an open vehicle window. If people sunbathing in the northern hemisphere tend to lie facing south in the morn-

Table 1 – Laterality of invasive cutaneous melanoma by population for selected countries, 1998–2003

Population	Number of cases		Left/right ratio	95% Confidence interval	
	Left	Right		Lower	Upper
Australia, NSW	6531	6034	1.08	1.04	1.12
England	10,345	9267	1.12	1.08	1.15
Finland	943	864	1.09	0.99	1.20
The Netherlands	6504	5839	1.11	1.07	1.16
Scotland	1667	1410	1.18	1.10	1.27
US SEER 'White'	25,348	23,469	1.08	1.06	1.10
Total	51,338	46,883	1.10	1.08	1.11

$\chi^2 = 9.94$, $P = 0.077$.
NSW, New South Wales; US SEER, United States Surveillance Epidemiology and End Results.

Table 2 – Laterality of invasive cutaneous melanoma by sex, age and selected sub-sites, for six populations combined, 1998–2003

	Number of cases		L/R ratio
	Left	Right	
All sub-sites combined			
Sex			
Male	24,095	21,967	1.10
Female	27,243	24,916	1.09
			$\chi^2 = 0.06$, $P = 0.804$
Age group (years)			
0–19	447	421	1.06
20–29	2353	2237	1.05
30–39	5652	5014	1.13
40–49	8371	7748	1.08
50–59	10,177	9264	1.10
60–69	9053	8270	1.09
70–79	9459	8600	1.10
⩾80	5826	5329	1.09
			$\chi^2 = 5.17$, $P = 0.639$
Total	51,338	46,883	1.10
Upper limb			
Sex			
Male	7267	6393	1.14
Female	8947	8027	1.11
			$\chi^2 = 0.73$, $P = 0.394$
Age group (years)			
0–19	123	128	0.96
20–29	680	639	1.06
30–39	1701	1488	1.14
40–49	2678	2429	1.10
50–59	3300	2927	1.13
60–69	3013	2717	1.11
70–79	2987	2657	1.12
⩾80	1732	1435	1.21
			$\chi^2 = 7.49$, $P = 0.380$
Total	16,214	14,420	1.12
Lower limb			
Sex			
Male	4139	3837	1.08
Female	11,484	10,387	1.11
			$\chi^2 = 0.89$, $P = 0.347$
Age group (years)			
0–19	139	142	0.98
20–29	878	769	1.14
30–39	2137	1789	1.19
40–49	2836	2677	1.06
50–59	3251	2925	1.11
60–69	2548	2390	1.07
70–79	2422	2235	1.08
⩾80	1412	1297	1.09
			$\chi^2 = 11.78$, $P = 0.108$
Total	15,623	14,224	1.10

ing, the left side of their body might be exposed and sunburned as the sun moves from east to west, making them more likely to cover up by afternoon. However, this would not explain the left-sided excess of cutaneous melanoma in New South Wales, Australia.

Fourthly, an excess of left-sided tumours might arise if there was a differential migration of melanocytes from the neural crest in the embryo, so that more end up on the left side of the body. But although many aspects of embryology are asymmetrical, the plausibility of this hypothesis is uncertain. We are not aware of any evidence that people have more benign nevi on the left side of their body, or that they tan unevenly (although perhaps this would not be perceptible). Furthermore, analysis of US SEER 'White' data for 1998–2003 does not demonstrate an excess of ocular melanomas on any particular side (left/right (L/R) ratio 0.97; 95% confidence intervals 0.88–1.06). A recent study has shown that the TGF-β superfamily member Nodal, a morphogen involved in several developmental functions including left-right asymmetry during embryogenesis, is secreted in aggressive melanomas of the skin.[5] Further analysis of US SEER 'White' data for 1998–2003 reveals a greater left-sided excess among tumours with distant metastases at diagnosis (L/R ratio 1.19, 95% confidence intervals 1.04–1.37), than among localised tumours (L/R ratio 1.09, 1.07–1.11) or tumours with regional spread (L/R ratio 1.06, 1.01–1.11). Nodal has been shown to promote tumorigenicity and plasticity in advanced melanomas, but is not expressed in normal skin or melanocytes. It is hypothesised that Nodal expression may be retained in a subpopulation of melanocytes migrating from the neural crest during embryogenesis, and that this same subpopulation may later become transformed as stem cell-like tumour cells.[6] A previous study demonstrated the presence of a subpopulation of stem cell-like tumour cells in approximately 20% of cultured metastatic melanomas.[7] If Nodal expression was retained asymmetrically in a small population of neural crest stem cells, this might explain the observed left-right ratio of incident cutaneous melanoma. Molecular typing of left- and right-sided cutaneous melanomas might generate support for this hypothesis, but pending further research, it remains speculative.

Finally, the excess of left-sided cutaneous melanomas could reflect asymmetry in the circulatory system resulting in differences in the capacity for angiogenesis, or asymmetry in response to DNA damage. However, we are not aware of any evidence that might support either of these phenomena.

In conclusion, we have observed an excess of left-sided cutaneous melanomas in several different populations. The excess seems unlikely to be explained by chance or recording bias. The most likely explanations would appear to be either differences in sun exposure and/or asymmetry of melanocyte distribution or characteristics arising at the time of embryological development.

Conflict of interest statement

None declared.

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