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Environmental risk factors for relapse of melanoma ☆

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ABSTRACT

Aim: To identify lifestyle factors affecting risk of relapse.
Methods: A comparison of 131 relapsed melanoma patients with 147 non-relapsers.
Results: Relapsers were more likely to report financial hardship using a number of different measures including access to holidays and feeling financially insecure (odds ratio (OR) 5.7, 95% confidence interval (CI) (1.5, 21.4)). Relapsers worked longer hours (mean 37 h per week compared with 31, $p = 0.02$). There was no reported difference in stress associated with recent life events. There was no effect of housing quality, employment factors or body mass index (BMI) on risk of relapse. There was a protective effect of antibiotics in the peri-operative period.
Conclusion: The study provides preliminary evidence for adverse effects of chronic financial hardship, but not recent stressful events on cancer relapse. As these data were collected in a retrospective case–control study subject to recall bias, the data must now be explored in a prospective study.

1. Introduction

Known predictors of survival in melanoma relate to characteristics of the tumour such as the Breslow thickness, mitotic rate and the presence of regression.[1] There are also host factors which correlate with risk, such as the tumour site and the patient's sex.[2] Little is known of other determinants of outcome, except that whilst melanoma is more common in those of high socioeconomic status, poorer survival is associated with deprivation.[3–5] A large study of older melanoma patients recently showed a lower risk of death from melanoma with higher socioeconomic status (hazard ratio 0.88 95% confidence interval (CI) (0.79, 0.98), $p = 0.02$) after adjusting for sex, age, stage at diagnosis, thickness, site, co-morbidity index and histology,[6] suggesting that poorer outcome in those of lower socioeconomic status was not caused by measurable diagnostic delay. Studying lifestyle in melanoma patients may give further insight into the components of deprivation affecting survival from cancer.

Melanoma is an immunogenic tumour: in that tumour infiltrating lymphocytes are usual in primaries, and absence of this immunological response to the tumour is a poor prog-

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nostic factor associated with a higher incidence of positive sentinel node biopsy.[7] The importance of immuno-competence to patients who have had melanoma was vividly illustrated by a case report in which two recipients of transplanted kidneys developed melanoma derived from the kidneys of the donor who had had melanoma 13 years previously.[8] Furthermore, rare spontaneous or chemotherapy-related remissions may occur in the context of immune-mediated vitiligo, when detectable immune responses to tumour antigens may be demonstrable.[9,10] Angiogenesis is also critical for the development of metastatic disease.[11,12] It is our hypothesis that lifestyle or life events associated with deprivation may influence survival by modulation of immune responses to the tumour or by effects on angiogenesis. That psychological stress might adversely affect host/tumour interactions has been postulated for some time but it has proved difficult to establish the validity of the hypothesis, not least because of the difficulty of measuring immunological changes in man which might mediate these effects. There are, however, some psychosocial data which provide evidence that stressful events and psychological distress may increase the risk of relapse in cancer, and here we reference two of the most recent.[13,14] Some human studies have reported that measurable changes in the immune system are associated with quality of life after cancer supporting the view that quality of life and competence of the immune system are linked.[15] There are also some data linking exposure to 'stressors' in animal studies which have been adopted because of the difficulties of designing human experiments focussed on variables which are complex and inter-related. So, recent murine models have looked at such things as pharmacological and physical stressors and promotion of metastases, and the effect of rehousing (social stress) on the effectiveness of chemotherapy[16,17] and reported evidence that at least in laboratory animals physical and social stress did appear to impact on host/tumour interaction.

In this hypothesis generating study, we also explored a number of additional different factors for which there was limited supportive evidence in the literature for an effect on relapse in order to inform the design of subsequent cohort studies. We, therefore, looked at body mass index (BMI) which has been reported to be associated with risk of melanoma[18] and exposure to incidental drugs such as statins[19]and L-Dopa.[20]

We designed a retrospective study of melanoma patients in the UK to identify candidate lifestyle factors having an effect on relapse. We postulated that, by interviewing melanoma patients who relapsed late from melanoma and patients who had not relapsed, we would identify relevant life events having an effect on host/tumour interaction and, therefore, relapse, occurring in the preceding years. This is a hypothesis generating study, which was, therefore, by intent one which has tested a large number of hypotheses.

2. Materials and methods

2.1. Patient recruitment

Recruitment took place between May 2000 and January 2005 from the Northern and Yorkshire, West Midlands, Oxford and Trent regions of the UK. Approval was obtained from regional and local ethics committees and the Patient Information Advisory Group (PIAG). Eligible patients ('relapsers' and 'non-relapsers') were recruited from the clinics of participating clinicians. The 'relapsers' were patients aged over 18 years at the time of recruitment with a melanoma >0.75 mm in thickness, who had suffered a relapse from that melanoma more than 3 years after removal of the primary tumour. 'Non-relapsers' were patients with a Breslow thickness >0.75 mm who had not relapsed at 5 or more years. In order to recruit long-term survivors who had been discharged from follow-up, we also identified eligible non-relapsers treated by the same doctors as the relapsers, using data from the cancer registries. Relapsers and non-relapsers were frequency-matched for age, sex and Breslow thickness.

The diagnostic histology sections from the primary tumours were examined (blind to case/control status) by AB, according to protocol. The following were recorded: Breslow thickness, tumour type, presence of ulceration, regression, mitotic rate, presence of tumour infiltrating lymphocytes (TILs) and excision margins. Regression was defined as the presence of scarring fibrosis, increased vascularity, a lymphocytic infiltrate and accumulation of melanophages.

2.2. Questionnaire data collection

Exposure data were collected using a specifically designed questionnaire, and the Hospital Anxiety & Depression Scale (HAD).[21] The HAD questionnaire was used as a measure of current psychological status. The new questionnaire was designed in order to collect specific information relating to deprivation, which was not necessarily identified using measures such as the Townsend score based upon postcode, or was related to perceptions of deprivation. Therefore detailed questions, for example, were asked about the participant's working life relating to whether the participants worked in shifts, how many hours per week they worked, and whether they found work stressful. Questions were asked about housing: relating to whether the participants felt that they had enough room in the house for their family, whether they felt that they had good neighbours and whether they felt safe at home. Participants were asked whether they had adequate access to recreational time at home or on holiday, and they were also asked to list hobbies or other pleasurable pursuits, and to indicate how much pleasure (out of a maximum score of 10) the most enjoyable activity gave them. Whilst pleasure resulting from hobbies may reflect current status rather than be related to long-term mental health, we were trying to test the hypothesis that positive or satisfying pastimes might be protective, just as chronic stress might be associated with an increased risk of relapse. In order to assess risk associated with stressful life events, participants were asked about life events potentially associated with psychological distress in the 5 years prior to interview such as serious illness in a loved one, miscarriage, divorce, bereavement, robbery or imprisonment. Participants were also asked to rank how the 'event' made them feel, from excellent to devastating on a 10-point scale. Some events might at first appear to be stressful such as a bereavement, but in some circumstances (for example, where the deceased person was suffering prior to death) loss

may be associated with net psychological benefit. We, therefore, attempted to measure the overall effect of his event using the scale.

Financial difficulties were assessed by asking questions about debts, redundancy and difficulties paying off loans. We also asked the participants whether they perceived that they were financially insecure, whether they felt able to take holidays as they wished and whether they felt they struggled to manage on their income and to pay for their car transport.

Data on alcohol intake and a brief smoking history were recorded. Self-reported height and weight were used to calculate a body mass index (BMI). We also used two postcode-based systems to give a measure of deprivation: the Townsend score[22] and the ACORN system (ACORN@CACI limited 2006).

Wound infections have been associated with increased risk of relapse for some cancers such as colon cancer[23] and therefore, data were collected on wound healing after excision of the primary, reported wound infections and the use of antibiotics around the time of surgery. In order to investigate the possibility that exposures might modulate the immune responses to cancer cells we asked about immunisation, blood transfusion and drug use. To investigate the effects of genetic variation in immune responses, we also asked the participants about their history of atopy or autoimmune disease.

We enquired about the use of incidental drugs of any kind except for occasional analgesia.

2.3. Statistical methodology

Two-sided *t*-tests were used for comparing continuous measures between relapsers and non-relapsers. Mann–Whitney *U* tests were used for non-normally distributed continuous measures. Spearman's correlations were calculated to explore relationships between non-normally distributed continuous variables. Associations between categorical variables and relapse status were tested for using chi-squared tests and logistic regression models. The data were also analysed in this way to compare the distribution of the variables in the cases who had relapsed less than 6.5 years post diagnosis to the cases who relapsed 6.5 or more years post diagnosis.

Multivariable logistic regression models were used to further explore any associations by adjusting for histological characteristics of the tumour and also age and sex. For some risk factors, analysis was restricted to relapsers interviewed within two years of relapse (80% of relapsers) to minimise the possibility that subjects were actually reporting the effects rather than the causes of relapse. All statistical analyses were carried out using STATA version 9 (StataCorp. 2005. Stata Statistical Software: Release 9. College Station, TX: StataCorp LP).

Table 1 – A case–control comparison of postcode-derived affluence scores (Townsend and ACORN), the Hospital Anxiety & Depression Scale (HAD) anxiety and depression scores, psychosocial indices and smoking histories

		Non-relapsers	Relapsers	*p*-Value
Sex[a]				
Female	*N* (%)	99 (67.4)	88 (67.2)	–
Male		48 (32.7)	43 (32.8)	
Age[a]				
Years	Mean (standard deviation, s.d.)	50.3 (14.3)	48.1 (14.3)	–
Breslow[a]				
mm	Median (range)	1.5 (0.8–13)	1.7 (0.8–20)	–
Townsend				
Score	Mean (s.d.)	0.3 (3.4)	0.3 (3.4)	1.0
Acorn				
Wealthy achievers	*N* (%)	49 (33.3)	43 (33.6)	0.9
Urban prosperity		14 (9.5)	15 (11.7)	
Comfortably off		68 (46.3)	54 (42.2)	
Moderate means		11 (7.5)	10 (7.8)	
Hard pressed		5 (3.4)	6 (4.7)	
HAD anxiety[b]				
Score	Mean (s.d.)	6.4 (3.6)	6.9 (3.9)	0.3
HAD depression[b]				
Score	Mean (s.d.)	3.2 (2.7)	3.6 (2.8)	0.2
Have you regularly smoked?[b]				
Yes	*N* (%)	58 (45.3)	45 (46.9)	0.8
Do you still smoke?[b]				
Yes	*N* (%)	16 (26.7)	14 (29.8)	0.7

a Not tested because frequency matching factor.
b Analysis restricted to the 104 relapsers who were interviewed within two years of relapse.

The sample size of the study gave 75% power to detect a factor with 30% frequency in non-relapsers, which doubles the risk of late relapse at a significance level of 5%. The power was reduced to 70% in analyses restricted to relapsers interviewed within two years of relapse. Because of the multiple hypotheses tested in this study, the nominal p-values quoted should not be interpreted at face value. A Bonferroni correction is not appropriate because of the correlation between many of the tests. Few results significant at the 0.5% level ($p < 0.005$) would be expected by chance, so findings significant at this level will be prioritised for confirmation in our ongoing prospective study of melanoma patients.

3. Results

424 patients were eligible for the study, of which 66% (278) participated. The participation rate was 79% in relapsers and 60% in non-relapsers. The median Breslow thickness was 1.6 mm (range 0.8–20) (Table 1). There was no effect of age on participation, but there was an effect of sex: 33% of participating relapsers were male compared with 59% of non-participating relapsers ($p = 0.005$), and 33% of participating non-relapsers were male compared with 26% of non-participating non-relapsers ($p = 0.2$). Participating relapsers were marginally more affluent than non-participating (mean Townsend scores 0.3 and 1.6, respectively, two-sided t-test, $p = 0.08$) but there was no difference for non-relapsers.

3.1. *Nature of the relapse in relapsers*

The median time from diagnosis to interview for non-relapsers was 8.0 years (range 5.0–31.7) and the median time to relapse for the relapsers was 6.6 years (range 3.0–28.1). There was no evidence of a relationship between Breslow thickness and time to relapse (rank correlation coefficient 0.01, $p = 0.9$). The median time to relapse did not differ by the site of primary (median 5.9 years, IQR (4.3–8.7) for axial tumours, median 6.9 years, IQR (4.5–11.3) for tumours on the limbs, $p = 0.2$ Mann–Whitney U test), although patients with tumours on the limbs were more likely to relapse very late (33% after 10 years) than those with axial tumours (19%).

3.2. *Histological findings*

There was no difference in the site of the primary between relapsers and non-relapsers (Table 2, $p = 0.8$), or in any other

Table 2 – Comparing the distributions of histological tumour characteristics and tumour site between relapsers and non-relapsers

	Non-relapsers N (%)	Relapsers N (%)	p-Value	Relapsers excluding systemic relapsers	p-Value
Site of primary					
Axial	48 (33.1)	47 (35.9)	0.6	37 (31.9)	0.8
Limb	97 (66.9)	84 (64.1)		79 (68.1)	
Ulceration					
No	112 (91.1)	85 (82.5)	0.1	74 (82.2)	0.1
Yes	11 (8.9)	18 (17.5)		16 (17.8)	
Tumour infiltrating lymphocytes					
None	6 (4.9)	5 (4.9)	0.3	5 (5.6)	0.4
Mild	59 (48.0)	59 (57.3)		52 (57.8)	
Non-brisk	31 (25.2)	26 (25.2)		21 (23.3)	
Brisk	27 (22.0)	13 (12.6)		12 (13.3)	
Regression					
No	91 (74.0)	75 (72.8)	0.8	65 (72.2)	0.8
Yes	32 (26.0)	28 (27.2)		25 (27.8)	
Initial incisional biopsy					
No	124 (85.5)	117 (90.7)	0.2	104 (90.4)	0.2
Yes	21 (14.5)	12 (9.3)		11 (9.6)	
Vertical growth phase					
No	10 (8.1)	3 (2.9)	0.1	3 (3.3)	0.1
Yes	113 (91.9)	100 (97.1)		87 (96.7)	
Mitotic rate[a]					
Mean (s.d.)	2.3 (3.4)	4.0 (5.9)	0.01	4.2 (6.2)	0.01
Vessel invasion[b]					
No	121 (98.4)	97 (94.2)	0.1	85 (94.4)	0.1
Yes	2 (1.6)	6 (5.8)		5 (5.6)	

p-Value from Pearson's chi-squared test for independence unless otherwise stated.
The number of missing data points ranges between 2 and 52 due to lack of histological information for some patients.
a Two-tailed t-test, mean and standard deviation reported.
b Fisher's exact test.

histological feature except for mitotic rate, which was higher in relapsers than in non-relapsers (4.0/mm^2 compared with 2.3/mm^2, two-sided t-test, $p = 0.01$). When restricting the analysis to the loco-regional relapsers ($N = 116$), to investigate possible variation according to the stage of disease, the results were unchanged. When all the histological criteria were considered in a multivariable analysis, none of the histological characteristics were significantly independently associated with relapse. Such is the importance of histological features in prognosis in larger data sets, however, that positive associations were adjusted for site, presence of ulceration, vertical growth phase, mitotic rate and vessel invasion.

3.3. *Deprivation scores*

The relapsers and non-relapsers did not differ in the mean postcode-derived deprivation score (Table 1). There was good correlation between the Townsend scores and the ACORN scores (Spearman's correlation coefficient 0.5, $p < 0.0001$) and the questionnaire-based deprivation measures (data not shown).

3.4. *Perceived financial hardship, housing and working*

Relapsers were significantly more likely to report that they did not feel 'financially secure', (OR = 5.7 for not secure versus secure, 95% CI (1.5, 21.4)). This association was strongest in people within the less affluent half of the population (using median Townsend score of –0.49 as the cut-off, Townsend $\geqslant$ –0.49 OR = 8.4, 95% CI (0.9, 76.7) for no versus yes and Townsend < –0.49 OR = 4.3, 95% CI (0.8, 22.9) for no versus yes). Relapsers were more likely to say that they struggle to run a car for financial reasons (OR = 3.8, 95% CI (1.5, 9.6)). Relapsers were marginally more likely to answer that they struggle on their income (OR = 2.9, 95% CI (1.4, 6.3) for 'struggle' versus 'comfortable'). Relapsers were more likely to say

Table 3 – Odds ratios and 95% confidence intervals for the effect of factors relating to perceived financial hardship on melanoma relapse

	Non-relapsers *N* (%)	Relapsers *N* (%)	Odds ratio (95% CI)	*p*-Value[a]
Financially secure				
Yes	71 (56.4)	46 (50.6)	1.0	0.02
Reasonably	52 (41.3)	34 (37.4)	1.0 (0.6, 1.8)	
No	3 (2.4)	11 (12.1)	5.7 (1.5, 21.4)	
Run a car				
Yes	112 (89.6)	72 (75.8)	1.0	0.005
Yes but struggle	7 (5.6)	17 (17.9)	3.8 (1.5, 9.6)	
No	6 (4.8)	6 (6.3)	1.6 (0.5, 5.0)	
Struggle on income				
Comfortable	66 (53.2)	36 (38.7)	1.0	0.02
Reasonable	43 (34.7)	33 (35.5)	1.4 (0.8, 2.6)	
Struggle	15 (12.1)	24 (25.8)	2.9 (1.4, 6.3)	
Ever made redundant				
No	95 (76.0)	65 (69.9)	1.0	0.3
Yes	30 (24.0)	28 (30.1)	1.4 (0.7, 2.5)	
Work shifts				
No	58 (79.5)	42 (80.8)	1.0	0.9
Yes	15 (20.5)	10 (19.2)	0.9 (0.3, 2.4)	
Earned more in past				
No	47 (37.6)	27 (29.4)	1.0	0.2
Yes	78 (62.4)	65 (70.7)	1.5 (0.8, 2.6)	
Unpaid credit card				
No	102 (80.3)	72 (76.6)	1.0	0.5
Yes	25 (19.7)	22 (23.4)	1.2 (0.7, 2.4)	
Mortgage payment difficulties				
No	123 (97.6)	91 (96.8)	1.0	0.7
Struggle	3 (2.4)	3 (3.2)	1.4 (0.3, 6.9)	
Take holidays where and when want				
Yes	86 (67.7)	52 (54.2)	1.0	0.001
Sometimes	35 (27.6)	23 (24.0)	1.1 (0.6, 2.0)	
No	6 (4.7)	21 (21.9)	5.8 (2.2, 15.3)	

Odds ratios and 95% confidence intervals from unadjusted analysis.
Analysis restricted to the 104 relapsers who were interviewed within two years of relapse.
The 'work shifts' factor was ascertained for the 125 patients currently employed.
The number of non-missing responses for the other factors ranges between 217 and 223.
a Likelihood ratio chi-squared *p*-value.

that they could not take holidays when and where they wish (OR = 5.8, 95% CI (2.2, 15.3) for 'no' versus 'yes'). The relapsers reported longer working hours than the non-relapsers (mean 37 h per week compared with 31 for the non-relapsers, two-sided *t*-test, $p = 0.02$). These associations persisted when adjusted for histological criteria. The models shown in Table 3 were repeated adjusting for age, and sex but this did not affect the results.

3.5. *Anxiety, depression and life events*

There was no difference in HAD scores between relapsers and non-relapsers: the mean anxiety score for non-relapsers was 6.4 and that for relapsers was 6.9 (two-sided *t*-test, $p = 0.3$, Table 1). Similarly, the mean depression score for non-relapsers was 3.2 and for relapsers it was 3.6 (two-sided *t*-test, $p = 0.2$).

Relapsers were marginally less likely to have experienced a serious illness in a loved one than the non-relapsers (27% and 38%, respectively, $p = 0.1$). Similarly, relapsers were less likely to have lost a loved one compared with non-relapsers (24% and 45%, respectively, $p = 0.001$) but there was no difference between relapsers and non-relapsers in the emotional effect this was reported to have on them ($p = 0.3$). There was no difference in other individual listed 'significant' life events. Overall, 71% of non-relapsers had experienced one or more adverse life-events compared with 58% of relapsers ($p = 0.03$). There was, however, no difference in the overall stress rating of these events in relapsers and non-relapsers.

The number of reported hobbies was highly variable: 11% overall reported none, whilst 20% reported 15 different hobbies or pleasurable activities. There was no difference between relapsers and non-relapsers in the number of

Table 4 – Odds ratios and 95% confidence intervals for the effect of exposures postulated to influence host/tumour interactions on melanoma relapse

	Non-relapsers *N* (%)	Relapsers *N* (%)	Odds ratio (95% CI)	*p*-Value[b]
Polio immunisation[a]				
Never/>5 years ago	105 (90.5)	76 (87.4)	1.0	0.5
In the last 5 years	11 (9.5)	11 (12.6)	1.4 (0.6, 3.4)	
Flu immunisation[a]				
Never/>5 years ago	69 (53.9)	48 (60.8)	1.0	0.3
In the last 5 years	59 (46.1)	31 (39.2)	0.8 (0.4, 1.3)	
Tetanus immunisation[a]				
Never/>5 years ago	92 (73.6)	76 (83.5)	1.0	0.1
In the last 5 years	33 (26.4)	15 (16.5)	0.6 (0.3, 1.1)	
Yellow fever immunisation[a]				
Never	112 (87.5)	84 (87.5)	1.0	1.0
Ever	16 (12.5)	12 (12.5)	1.0 (0.4, 2.2)	
Any immunisation in the last 5 years[a,c]				
No	29 (25.0)	26 (33.8)	1.0	0.2
Yes	87 (75.0)	51 (66.2)	0.7 (0.3, 1.2)	
Use of any drugs after diagnosis				
No	85 (57.8)	87 (66.4)	1.0	0.1
Yes	62 (42.2)	44 (33.6)	0.7 (0.4, 1.1)	
Use of statins				
No	144 (98.0)	123 (93.9)	1.0	0.1
Yes	3 (2.0)	8 (6.1)	3.1 (0.8, 12.0)	
Any oestrogen				
No	141 (95.9)	126 (96.2)	1.0	0.9
Yes	6 (4.1)	5 (3.8)	0.9 (0.3, 3.1)	
Wound healing problems after primary				
No	115 (80.4)	99 (82.5)	1.0	0.7
Yes	28 (19.6)	21 (17.5)	0.9 (0.5, 1.6)	
Skin graft for primary				
No	77 (60.2)	68 (58.1)	1.0	0.7
Yes	51 (39.8)	49 (41.9)	1.1 (0.7, 1.8)	
Antibiotics after surgery				
No	109 (76.2)	108 (90.0)	1.0	0.003
Yes	34 (23.8)	12 (10.0)	0.4 (0.2, 0.7)	

Odds ratios and 95% confidence intervals from unadjusted analysis.

a Analysis restricted to the 104 relapsers who were interviewed within two years of relapse.

b Likelihood ratio chi-squared *p*-value.

c Based on immunisations against polio, flu, pneumonia, hepatitis A, hepatitis B, bacilli Calmette-Guerin (BCG), meningitis and tetanus.

reported hobbies, but the relapsers reported less pleasure associated with those hobbies (two-sided *t*-test, $p = 0.01$). There was a negative correlation between the number of reported hobbies and the HAD depression score, so that the more hobbies were reported the less depressed the score (Spearman correlation coefficient –0.1, $p = 0.06$).

The mean BMI for relapsers was 25.4 compared with 25.7 for non-relapsers (two-sided *t*-test, $p = 0.7$). Relapsers and non-relapsers did not differ in reported alcohol intake or smoking history.

3.6. *Factors potentially related to host–tumour interaction*

2% of relapsers and 3% of non-relapsers reported having an auto-immune-mediated disease post diagnosis of the primary melanoma. 4% of relapsers reported any atopic disease post diagnosis of the primary melanoma compared with 2% of non-relapsers.

There was no difference between relapsers and non-relapsers in their history of recent (within 5 years) immunisation against polio (13% and 10%, respectively), flu vaccine (39% and 46%, Table 4), pneumonia (8% and 13%), hepatitis A (10% and 9%) or hepatitis B (6% and 5%). There was a marginal difference for recent immunisation against tetanus: 17% of relapsers had been immunised against tetanus within the previous 5 years compared with 26% of non-relapsers. In the 5 years before recruitment, one participant had been immunised against bacilli Calmette-Guerin (BCG) and none had been immunised against meningitis. Overall, 66% of the relapsers had had one or more vaccine in the 5 years before interview compared with 75% of the non-relapsers.

42% of the relapsers had had a skin graft at the time of excision of the primary, compared with 40% of the non-relapsers. The relapsers reported a median time to heal the graft of 21 days compared with 14 days in the non-relapsers (Mann–Whitney *U* test, $p = 0.1$). Wound healing problems were reported in 18% of relapsers and 20% of non-relapsers. Relapsers were less likely to have been given antibiotics around the time of excision of the primary: 10% of the relapsers had antibiotics compared with 24% of the non-relapsers (OR 0.4, 95% CI (0.2, 0.7), $p = 0.003$). This association remained when correcting for Breslow thickness of the primary tumour (adjusted OR 0.3, 95% CI (0.2, 0.7)). Enquiry revealed that in some hospitals, antibiotic prescription was used prophylactially after some surgical procedures such as skin grafting.

34% of the relapsers had taken at least one incidental therapeutic drug regularly post diagnosis of the primary melanoma compared with 42% of the non-relapsers. 6% of relapsers had taken statins compared with 2% of the non-relapsers. None of the participants had taken L-Dopa. There was no difference in exposures to non-steroidal anti-inflammatory drugs (6% of the relapsers compared with 4% of the non-relapsers) or to immuno-suppressant drugs (5% of both relapsers and non-relapsers).

3.7. *Time to relapse*

To eliminate the possibility of heterogeneity between the relapsers who relapsed very late after the primary melanoma and those who relapsed soon after the primary melanoma, the relapsers were stratified by the median time to relapse (6.5 years) and the distributions of the significant findings above were compared between these two groups. None of the potential risk factors found in this study significantly differed between those who relapsed less than 6.5 years post diagnosis and those who relapsed 6.5 or more years post diagnosis.

4. Discussion

Deprivation has been reported to reduce survival rates from melanoma[3,6] as it has for many cancers.[24,25] We found no significant difference between late relapsers and non-relapsers in terms of their postcode-derived deprivation score or in reported material effects of deprivation such as reported poor housing, obesity, smoking and alcohol abuse. Relapsers were, however, more likely to report perceived financial hardship than were non-relapsers. The consistency of reported financial difficulties, related to several aspects of paucity of resources, and the lack of detected differences in other aspects of lifestyle are of note. A lack of difference in HAD score between relapsers and non-relapsers suggests that clinical depression or anxiety did not explain these differences. Relapsers reported that they were no more likely to have suffered a fall in income which suggests that their perceptions about finances did not reflect a recent loss of employment as a result of the relapse. It remains possible, however, that these observations reflect recall bias or a perception that things might be harder in the future as a result of the relapse. Although these findings are of note therefore, they cannot yet be interpreted: rather they will now be addressed prospectively in a cohort study.

We report a hypothesis generating study designed to identify possible environmental factors associated with relapse from melanoma. We chose a case–control study design as a reasonable approach to hypothesis generation, in order to inform the design of much more expensive cohort studies. There are many problems, however, inherent in case–control studies around bias of recall but in epidemiological studies addressed to cancer aetiology, they have proved very effective and generally speaking have identified risk factors validated in subsequent cohort studies. In the melanoma field, for example, case–control studies identified sun burn and sun sensitive phenotypes as the key risk factors for melanoma[26] as was confirmed in a Nordic cohort study.[27] Thus a case–control study is a reasonable approach to the identification of potentially important new exposures which may be causal for or protective of relapse. One of the measures identified by this study, however, was perceived financial hardship and whilst this is potentially a real finding, psychosocial factors are likely to be especially subject to basis of recall and therefore this finding must be viewed with some caution.

The means by which perceived financial hardship might impact on survival is unknown but it is postulated to be mediated by stress-induced immune suppression.[28,29] The Townsend score uses census data on unemployment, overcrowding, non-car ownership and non-home ownership, based upon small enumeration districts to compute a ranked score[22] for material deprivation. It has been shown to be

sensitive enough to correlate with survival and clinical events such as postoperative mortality[22] for other cancers but in this study did not predict case–control status. We matched for Breslow thickness because it is a known predictor of survival, but this could have removed some of the effect of socioeconomic status in our study. Our observations may suggest that direct questioning about material deprivation is more sensitive than postcode-derived measures or that it is the perception of financial hardship that is the key predictor. Lack of money and the impact that has on empowerment and psychological stress may be more important than specific effects on living conditions such as overcrowding. Although more affluent patients were more likely to take part in the study overall, proportionally fewer relapsers from deprived areas took part than non-relapsers so that any recruitment bias is likely to have reduced the size of the effect seen rather than to increase it. Moreover, in this study we matched for Breslow thickness at diagnosis to reduce the effect of any deprivation-related treatment delay.

We postulated that recent stressful life events might increase the risk of relapse from melanoma, but the study produced no support for a role for these in the late relapse. Our study did provide support for the view that melanoma patients might be more subject to adverse effects from financial stress (assumed to be chronic) than 'recent significant' life events. It was postulated that psychological stress has a negative effect on survival from cancer as a result of immune suppression as suggested by others,[28,29] although this remains a controversial concept. Studying immune changes as a result of psychological changes is inherently difficult and some researchers have used animal models to address this. A recent study, for example, suggested that in mice, immune suppression resultant from stress induced by restraint, is mediated by toll-like receptor 4[30] and there are a number of murine studies in which mice with components of the immune system knocked out responded differently to stressors that wild type mice.[31] Whilst the issue remains under investigation, there are, therefore, data to support a relationship between psychological stress and immune suppression and as melanoma is an immunogenic tumour the possibility that psychological stress in some form might have a deleterious effect on survival remains a possibility. Furthermore, there are data to support the view that chronic stress appears to result in suppression of the immune response, whereas both immune activation and suppression have been associated with acute stress.[32,33] Our study provided little evidence for a protective effect of support or hobbies but this will be better addressed in a prospective study.

We further hypothesised that exposures which reduce cell-mediated responses (such as smoking and immuno-suppressant drugs) may be risk factors for relapse,[34] but no evidence for this was found in an albeit small study. There is evidence that Th1-type immune responses are modulated in life in response to immunisation and infection, and there are data to support the view that these exposures, particularly in early life, may influence the subsequent development of diseases such as atopy.[35] This prompted others working on melanoma to explore the possibility that vaccination may be protective for melanoma, and Pfahlberg and colleagues showed that previous bacilli Calmette-Guerin (BCG) was protective for melanoma risk.[36] We found no evidence for a relationship between past medical history or immunisation and risk of relapse. The study was, however, insufficiently powered to exclude significant relationships of this sort.

Wound healing is characterised by reduced cellular immunity and new blood vessel formation, and delayed wound healing results in chronic inflammation. The importance of new blood vessel formation and chronic inflammation in the promotion of cancer was reviewed by Dalgleish.[37] The apparent protective effect of antibiotics around excision of the primary tumour in this study is of interest. It is possible that the use of antibiotics might reduce an infection-related drive to angiogenesis, although it is likely that this was a chance finding. It will be addressed, however, in a prospective study.

This study has identified some life-style factors, which might be important as components of deprivation-related moderation of survival. There was evidence that perceived financial difficulty was related to risk of relapse, whereas more acute adverse life events appeared not to be. There was evidence to support the view that exposure to antibiotics used at the time of surgery for primary melanoma was protective for relapse.

This was a hypothesis generating study. It was small and retrospective and subject to multiple testing. The conclusions drawn may therefore be subject to bias and must be explored in larger prospective studies. The study does, however, provide a basis for those prospective investigations.

Conflict of interest statement

None declared.

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REFERENCES

1. Clark Jr WH, Elder DE, Guerry DT, et al. Model predicting survival in stage I melanoma based on tumor progression. *J Natl Cancer Inst* 1989;**81**(24):1893–904.
2. Elder D, Murphy G. Malignant tumors (melanomas and related lesions). In: Atlas of tumor pathology: melanocytic tumors of the skin, vol. 2 (third series); 1991. p. 103–205.

3. MacKie RM, Hole DJ. Incidence and thickness of primary tumours and survival of patients with cutaneous malignant melanoma in relation to socioeconomic status. *BMJ* 1996;**312**(7039):1125–8.
4. Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993–2003. *Br J Cancer* 2006;**95**:91–5.
5. Coleman MP, Rachet B, Woods LM, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *Br J Cancer* 2004;**90**(7):1367–73.
6. Reyes-Ortiz CA, Goodwin JS, Freeman JL, Kuo YF. Socioeconomic status and survival in older patients with melanoma. *J Am Geriatr Soc* 2006;**54**(11):1758–64.
7. Taylor RC, Patel A, Panageas KS, Busam KJ, Brady MS. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. *J Clin Oncol* 2007;**25**(7):869–75.
8. MacKie RM, Reid R, Junor B. Fatal melanoma transferred in a donated kidney 16 years after melanoma surgery. *New Engl J Med* 2003;**348**(6):567–8.
9. Cui J, Bystryn J-C. Melanoma and Vitiligo are associated with antibody responses to similar antigens on Pigment cells. *Arch Dermatol* 1995;**131**:314–8.
10. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastitic melanoma. *Nature Med* 1998;**4**(3):321–7.
11. Flaherty KT. New molecular targets in melanoma. *Curr Opin Oncol* 2004;**16**(2):150–4.
12. Jendreyko N, Popkov M, Rader C, Barbas 3rd CF. Phenotypic knockout of VEGF-R2 and Tie-2 with an intradiabody reduces tumor growth and angiogenesis in vivo. *Proc Natl Acad Sci USA* 2005;**102**(23):8293–8.
13. Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. *Breast Cancer Res Treat* 2007;**105**(2):209–19.
14. Palesh O, Butler LD, Koopman C, Giese-Davis J, Carlson R, Spiegel D. Stress history and breast cancer recurrence. *J Psychosom Res* 2007;**63**(3):233–9.
15. Nelson EL, Wenzel LB, Osann K, et al. Stress, immunity, and cervical cancer: biobehavioral outcomes of a randomized clinical trail. *Clin Cancer Res* 2008;**14**(7):2111–8.
16. Rosenne E, Shakhar G, Melamed R, Schwartz Y, Erdreich-Epstein A, Ben-Eliyahu S. Inducing a mode of NK-resistance to suppression by stress and surgery: a potential approach based on low dose of poly I-C to reduce postoperative cancer metastasis. *Brain Behav Immun* 2007;**21**(4):395–408.
17. Kerr LR, Andrews HN, Strange KS, Emerman JT, Weinberg J. Temporal factors alter effects of social housing conditions on responses to chemotherapy and hormone levels in a Shionogi mammary tumor model. *Psychosom Med* 2006;**68**(6):966–75.
18. Dennis LK, Lowe JB, Lynch CF, Alavanja MC. Cutaneous melanoma and obesity in the Agricultural Health Study. *Ann Epidemiol* 2008;**18**(3):214–21.
19. Jakobisiak M, Golab J. Potential antitumor effects of statins (Review). *Int J Oncol* 2003;**23**(4):1055–69.
20. Factor SA. Current status of symptomatic medical therapy in Parkinson's disease. *Neurotherapeutics* 2008;**5**(2):164–80.
21. Zigmund A, Snaith R. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
22. Smith JJ, Tilney HS, Heriot AG, et al. Social deprivation and outcomes in colorectal cancer. *Br J Surg* 2006;**93**(9):1123–31.
23. Nespoli A, Gianotti L, Bovo G, Brivio F, Nespoli L, Totis M. Impact of postoperative infections on survival in colon cancer patients. *Surg Infect (Larchmt)* 2006;**7**(Suppl. 2):S41–3.
24. Kaffashian F, Godward S, Davies T, Solomon L, McCann J, Duffy SW. Socioeconomic effects on breast cancer survival: proportion attributable to stage and morphology. *Br J Cancer* 2003;**89**(9):1693–6.
25. Coleman MP, Babb P, Sloggett A, Quinn M, De Stavola B. Socioeconomic inequalities in cancer survival in England and Wales. *Cancer* 2001;**91**(1 Suppl):208–16.
26. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005;**41**(1):45–60.
27. Veierod MB, Weiderpass E, Thorn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst* 2003;**95**(20):1530–8.
28. Reiche EM, Morimoto HK, Nunes SM. Stress and depression-induced immune dysfunction: implications for the development and progression of cancer. *Int Rev Psychiatry* 2005;**17**(6):515–27.
29. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann NY Acad Sci* 1999;**896**:30–47.
30. Zhang Y, Woodruff M, Miao J, Hanley G, Stuart C, Zeng X, et al. Toll-like receptor 4 mediates chronic restraint stress-induced immune suppression. *J Neuroimmunol* 2008;**194**(1–2):115–22.
31. Engler H, Bailey MT, Engler A, Stiner-Jones LM, Quan N, Sheridan JF. Interleukin-1 receptor type 1-deficient mice fail to develop social stress-associated glucocorticoid resistance in the spleen. *Psychoneuroendocrinology* 2008;**33**(1):108–17.
32. Maddock C, Pariante CM. How does stress affect you? An overview of stress, immunity, depression and disease. *Epidemiol Psychiatr Soc* 2001;**10**(3):153–62.
33. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004;**130**(4):601–30.
34. O'Byrne KJ, Dalgleish AG, Browning MJ, Steward WP, Harris AL. The relationship between angiogenesis and the immune response in carcinogenesis and the progression of malignant disease. *Eur J Cancer* 2000;**36**(2):151–69.
35. Marks GB, Ng K, Zhou J, et al. The effect of neonatal BCG vaccination on atopy and asthma at age 7 to 14 years: an historical cohort study in a community with a very low prevalence of tuberculosis infection and a high prevalence of atopic disease. *J Allergy Clin Immunol* 2003;**111**(3):541–9.
36. Pfahlberg A, Kolmel KF, Grange JM, et al. Inverse association between melanoma and previous vaccinations against tuberculosis and smallpox: results of the FEBIM study. *J Invest Dermatol* 2002;**119**(3):570–5.
37. Dalgleish AG, O'Byrne KJ. Chronic immune activation and inflammation in the pathogenesis of AIDS and cancer. *Adv Cancer Res* 2002;**84**:231–76.