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3 **Associations between bullous pemphigoid and**

4 **primary malignant cancers: an English national record**

5 **linkage study, 1999–2011**

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ABSTRACT

We conducted a nationwide record-linked study using all English NHS hospital admission data and mortality statistics from 1999 to 2011 to evaluate the risk of concurrent or subsequent bullous pemphigoid (BP) in a cohort of 2,873,720 individuals with malignant cancers, compared with a reference cohort. We calculated standardised rate ratios (RRs) based on person-years at risk, comparing the observed and expected numbers of BP cases in the cancer cohort with those in the reference cohort. Overall, the cohort of people with a record of a malignant cancer was not found to be at greater risk of concurrent or subsequent BP than the cohort of people without a record of a malignant cancer (RR 0.96, 95% CI 0.88 to 1.04), although elevated risks of BP were found in sub-cohorts of people with either kidney cancer, laryngeal cancer or lymphoid leukaemia. We also similarly analysed the risk of concurrent and subsequent malignant cancers in a cohort of people with a principal diagnosis of BP, and again found no increased risk compared with the reference cohort (RR 1.00, 95% CI 0.92 to 1.09).

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INTRODUCTION

Bullous pemphigoid (BP) is a rare autoimmune bullous skin disease characterized by an autoimmune response to hemidesmosomal proteins within the dermo-epidermal junction (BP180 and BP 230) [7]. There is mixed evidence on whether BP is more common among people with a history of malignant cancer than in those without. Some case control studies have not found significant associations with malignancy [6, 11, 18]. Other studies have found significantly increased risks of cancers as co-morbidity with BP, and some authors have recommended detailed examination and screening for internal malignancy in all patients diagnosed with BP [3, 5, 14, 16]. BP is rare, so large studies are needed to study associations between it and cancers. Most previous studies have, however, been statistically underpowered to report reliably on such associations.

We used a linked national English hospital admission and mortality dataset for all public hospitals in England between 1999 and 2011. The size of our dataset and our methods of analytical modelling allowed us to determine whether BP occurs in individuals with a history of malignancy more or less often than expected.

MATERIALS AND METHODS

Population and data

The dataset comprised statistical information on all National Health Service hospital day cases and admissions, and on all deaths, in the whole of England from 1st January 1999 to 28th February 2011. The hospital data are from English national Hospital Episode Statistics (HES) supplied by the English national Information Centre for Health and Social Care. The mortality data derive from death certificates and were supplied by the Office for National Statistics. Both sets of data contain diagnosis codes using the International Classification of Diseases 10th Revision (ICD-10). Successive records for each individual were linked together, and the dataset constructed for analysis, by the Oxford record linkage group.

BP in people with cancer

We constructed a cohort of people with a diagnosis of any malignant cancer (the “cancer cohort”) by identifying the first episode of day case care, or admission, for any malignant cancer during the study

period. People were included in the cancer cohort if, first, they had a hospital record containing a diagnosis code within the range ICD-10 C00-C97 specified in the principal position on the hospital record, and, second, they had no prior record of BP. As in previous studies of disease associations by our group [17], a “reference cohort” was also constructed for comparison. This cohort comprised individuals who did not have a record of cancer, whose principal diagnosis at admission was for one of a wide range of reasons listed in the footnotes to Table 2, and who also did not have a prior record of BP. The reference cohort consisted of conditions known not to have a significant association with either cancer or BP. The individuals in the cancer cohort and reference cohort were then “followed up” by searching the database for any record of subsequent, or co-occurring, care for, or death from, BP (ICD-10 L12.0).

Using the same methods as above, we then carried out sub-analyses to determine whether cohorts of people with specific malignant cancers (listed in Table 2) had higher rates of BP than expected when compared with the reference cohort.

Statistical methods

Rates of BP in the cancer cohort and the reference cohort were calculated based on person-days of “follow-up”. Date of entry into each cohort was the date of first admission for the cancer, or reference condition, and date of exit was the date of first record of BP, death, or the end of the study period (31 December 2011), whichever was the earliest. We stratified each cohort by age (in five-year age groups), sex, calendar year of first recorded admission, region of residence, and quintile of patients’ Index of Deprivation score (a standard English measure of socio-economic status), to obtain observed numbers of BP in each stratum of the cancer cohort and the reference cohort. The indirect method of standardisation was then used, taking the cancer cohort and reference cohort combined as the standard population. We applied the stratum-specific rates of BP in the standard population to the person-days in each corresponding stratum of, first, the cancer cohort and, second, the reference cohort, to obtain the expected number of people with BP in each stratum of each of the two cohorts. Expected numbers were then summed across strata to give the ‘expected’ total number of BP in each of the two cohorts. The standardised rate ratio for BP in the cancer cohort, compared with the reference cohort, was calculated using the formula (O^{CAN}/E^{CAN}) divided by (O^{REF}/E^{REF}) , where O^{CAN} and E^{CAN} are the observed and expected

numbers of BP in the cancer cohort and O^{REF} and E^{REF} are the observed and expected numbers of BP in the reference cohort. 95% confidence intervals for the rate ratios and χ^2 statistics for significance were calculated as described elsewhere [2]. We applied post-hoc Bonferroni corrections for multiple comparisons, where findings were significant at $p < 0.05$, to allow for familywise error in the cohort analyses of individual cancers. Continuity corrections, for small numbers, were used.

Cancer in people with BP

We conducted a separate cohort analysis, this time taking people with BP as the principal diagnosis on the record (the “BP cohort”) and following them up by searching the database for any subsequent, or co-occurring care for, or death from, cancer. By requiring that BP always be the ‘principal’ diagnosis on the HES record, or, in the case of a death record, the ‘underlying cause’, we avoided overlap between the co-occurring cases in this analysis and those in the analysis of BP in the cancer cohort (where we required that cancer always be the principal diagnosis or underlying cause). Standardised rate ratios were calculated in the same way as described above, to determine whether the rate of cancer in the cohort of people with BP differed significantly from the rate of cancer in the cohort of people without BP. We compared the BP cohort against the reference cohort to determine rate ratios for ‘any’ cancer diagnosis within the range ICD-10 C00-C97, and to determine rate ratios for the specific cancers listed in Table 2.

RESULTS

The cohorts

Table 1 shows the number, age and sex distribution of people in the BP cohort and the ‘any cancer’ cohort. The reference cohort comprised over 5.5 million people, and there were ample people to populate every cell in the model used to produce the stratum-standardised rate ratios.

BP in the cancer cohorts

Altogether, out of 2.87 million people with a principal diagnosis of cancer, 917 also had a diagnosis of BP on either the same or a subsequent record during the study period (Table 2).

People with a principal diagnosis of cancer were, overall, no more likely than the reference cohort to have a concurrent or subsequent diagnosis of BP: comparison of the two cohorts showed a rate ratio of 0.96 (95%CI 0.88 to 1.04) (Table 2). Taking significance at $p < 0.05$, high rate ratios were found in three cancer sub-cohorts– those comprising people with cancers of the kidney , RR 2.23 (95%CI 1.48 to 3.24, $p < 0.001$; $n=28$); cancers of the larynx RR 2.22 (1.21 to 3.75, $p=0.004$; $n=14$); and lymphoid leukaemia , RR 2.27 (1.21 to 3.89, $p=0.005$; $n=13$). A marginally low rate ratio was found when considering one individual cancer cohort – that which comprised people with breast cancer , RR 0.77 (0.60 to 0.98, $p=0.04$; $n=71$). After applying a post-hoc Bonferroni correction for multiple comparisons, by dividing the 0.05 level of significance by the number of cancer types studied ($0.05/31 = 0.0016$), only the rates of BP in people with kidney cancer remained significantly high compared with the reference cohort.

Cancers in the BP cohort

In the cohort of 4720 people with a principal diagnosis of BP, 502 had a concurrent or subsequent record of a malignant cancer (C00-C97) during the study period (Table 2).

Comparing the BP cohort with the reference cohort, the RR for concurrent or subsequent malignant cancer was 1.00 (95 CI 0.92 to 1.09), showing no overall significant association. Taking significance at $p < 0.05$, the BP cohort differed from the reference cohort in relation to only one individual cancer – lymphoid leukaemia – where the rate ratio was 1.91 (95% CI 1.15 to 2.99 $p=0.007$, Table 2). After Bonferroni correction for multiple comparisons, this RR ceases to be statistically significant.

DISCUSSION

Principal Findings

We find no overall association between cancer and BP on a population level.

With 4720 BP cases and 2,873,720 cancer cases in our initial cohorts, this is a very large epidemiological study of the relationship between BP and cancer. This is particularly important given the rarity of BP, which has an incidence of 4.3 per 100,000 person years [9]. Even in our national study, statistical power in relation to some of the analyses of individual cancers was fairly weak. However, we report the results in

detail both for the record and in the hope that they may be useful to investigators studying the pooled world literature on individual cancers and BP in either systematic review or meta-analysis.

BP in the cancer cohorts

At the significance level of $p < 0.05$, we found high rates of BP in 3 out of 31 individual cohorts (kidney cancer, laryngeal cancer and lymphoid leukaemia). Lymphoid leukaemia and laryngeal cancers have been previously noted in other studies to have a positive association before BP [3]. After correcting for multiple comparisons, only the rates of BP in the kidney cancer cohort remained significantly high; but acceptance of the Bonferroni correction may be a conservative interpretation of the association found by us between BP and the other two cancers. On the one hand, the Bonferroni correction makes allowance for multiple comparisons. On the other, it risks dismissal of real associations simply because it sets the bar so high that, in analyses of small numbers (as with lymphoid leukaemia and laryngeal cancer), there is not the power to attain the very high levels of significance required after correction.

We can only speculate on the potential mechanism for the association between BP after kidney cancer. It might be that certain treatment regimes for kidney cancer or pathology relating to the kidney itself might predispose to BP. Case-control studies and case reports suggest that certain renally acting drugs like loop diuretics [12], ACE inhibitors [15] and spironolactone [1], are associated with the development of BP. Potentially renotoxic drugs like non-steroidal anti-inflammatory drugs [4, 8] have been reported to be associated with BP. There have also been case reports of BP in renal transplant patients [10]. Due to privacy regulations, unfortunately, we cannot seek access to details of treatment regimes from patient notes.

Cancers in the BP cohort

Comparing the rates of 31 individual cancer types in the BP cohort with those in the reference cohort, we did not find significantly high or low rate ratios in respect of any cancer after correcting for multiple comparisons.

A recent study showed an increased risk of cancer in patients with BP who are treated with immunosuppressive agents like azathioprine, cyclophosphamide, cyclosporine or mycophenolate mofetil compared to BP patients treated with systemic corticosteroids only [13]. However, the cancers most associated with immunosuppression are those of the skin and lymphomas [20]. We do not see this pattern, although the rate ratio for lymphoid leukaemia, which is statistically high before correcting for multiple comparisons, at the level of $p=0.007$, cannot be dismissed entirely as a chance finding.

Relation to Previous Work

In Britain, a small case-control study of 84 BP patients found increased malignancy risk based on 15 individuals with cancer in the BP group [19]. Increased risks have also been seen in a Polish population in 110 BP patients [3]. However, much of the previous work on this subject has been carried out in Japan. To date, the largest study comprised a total of 1113 BP patients in Japanese hospitals [16]. It reported a significantly increased chance of contracting cancer after BP, and concluded that screening for internal malignancy is essential for all patients with BP. These increased risks were corroborated in another Japanese study of 204 BP and PV patients [5]. Differences between British and Japanese populations, for example in relation to lifestyle, environment or genes, might account for the difference between our results and those of the Japanese studies.

Strengths and Weaknesses

Our results rely on the accuracy with which autoimmune bullous skin disorders and cancers are diagnosed in hospital practice and coded in routine hospital administrative datasets. We had no access to original clinical records or to laboratory confirmation or disease severity, anatomical location or clinical presentation. Our study was limited to patients who had an episode of hospital day-case care or admission in a public hospital in England or who died within the study period. These patients might differ systematically in terms of cancer risk when compared to patients with milder episodes not warranting hospital admission. None the less, we suggest that this is an unlikely source of bias, because, if there is a true cancer risk, it seems likely that, if anything, it would be higher in patients with serious enough bullous disease to warrant hospital care. However, in studies that have considered this, no associations have been

found between cancer risk and circulating antibody titre levels or extent of mucosal involvement [16] or severity of BP [5].

Our dataset, though large, is fairly modest in the range of variables it includes. Our conclusions should be regarded as speculative rather than definitive. However, the overall rate ratios, both when looking at the rate of cancer in people with BP and at the rate of BP in people with cancer, are very close to 1, with moderately narrow confidence intervals. The effect of any important unmeasured confounders, should they exist, would have to be equal and opposite to any true degree of positive or inverse association.

Conclusion

Contrary to some previous studies, we find no evidence of increased risk of BP in people with cancer overall, and no evidence of increased risk of cancer overall in people with BP. We do, however, find an increased risk of BP in people who have one of a few specific cancers, most notably renal cancer. The suggestion that people with BP in European countries, or populations of European origin, should be selectively screened for cancer needs further evidence to determine whether it is warranted.

237 *Conflict of Interest*

238 The authors state no conflict of interest

239

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250 *Ethical approval*

251 Ethical approval for analysis of the record linkage study data was obtained from the Central and South

252 Bristol Multi–Centre Research Ethics Committee (04/Q2006/176).

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Table 1: Age-distribution of people in the malignant cancer cohort (ICD10 C00-C97) and, separately, in the BP cohort (L12.0), and the percentage who were female

Age at admission	Number in cancer cohort (% of total)	% female	Number in BP cohort (% of total)	% female
0-14	13907 (0.5)	46.4	7 (0.1)	28.6
15-19	7877 (0.3)	43.7	5 (0.1)	80
20-24	12024 (0.4)	46.3	5 (0.1)	40
25-29	19936 (0.7)	53.3	6 (0.1)	83.3
30-34	32113 (1.1)	58.8	10 (0.2)	60
35-39	51627 (1.8)	63.6	17 (0.4)	64.7
40-44	80175 (2.8)	65.3	20 (0.4)	60
45-49	117174 (4.1)	63.6	49 (1)	44.9
50-54	179733 (6.3)	60.4	85 (1.8)	50.6
55-59	247807 (8.6)	53.2	128 (2.7)	46.9
60-64	324998 (11.3)	48.8	143 (3)	49
65-69	372205 (13)	45	257 (5.4)	45.9
70-74	406252 (14.1)	44	527 (11.2)	49.3
75-79	413947 (14.4)	45.3	840 (17.8)	51.8
80-84	321311 (11.2)	48.8	1049 (22.2)	56.9
85+	272634 (9.5)	56.6	1572 (33.3)	67
All ages	2873720 (100)	50.4	4720 (100)	57.2

Table 2: Observed numbers (O) of admissions for cancer in the BP cohort, and for BP in the cancer cohort during the study period 1999-2011; expected numbers (E) based on comparison with the reference cohort¹; rate ratios² (RR) and their 95% confidence intervals

Cancer site (ICD-10 code)	BP in the cancer cohort			Cancer in the BP cohort		
	O	E	RR (95% CI)	O	E	RR (95% CI)
Any cancer (C00-C97)	917	939.6	0.96 (0.88-1.04)	502	501	1.00 (0.92-1.09)
Bladder (C67)	109	97.5	1.13 (0.92-1.37)	46	34.5	1.33 (0.98-1.78)
Bone (C40-C41)	2	1.4	1.40 (0.17-5.05)	2	1.2	1.70 (0.21-6.17)
Brain (C71)	10	6.4	1.57 (0.75-2.89)	2	5.7	0.35 (0.04-1.27)
Breast (C50)	71	90.7	0.77 (0.60-0.98)	39	44.1	0.88 (0.63-1.21)
Cervix (C53)	4	3	1.34 (0.37-3.45)	3	2.2	1.36 (0.28-3.99)
Colon (C18-C19)	92	86.4	1.07 (0.86-1.32)	50	50.9	0.98 (0.73-1.30)
GI - upper (C00-C06-8, C09-C10, C12-C14)	8	9.8	0.81 (0.35-1.60)	9	5	1.80 (0.82-3.41)
Kidney (C64-C65)	28	12.7	2.23 (1.48-3.24)	10	11.6	0.86 (0.41-1.59)
Larynx (C32)	14	6.3	2.22 (1.21-3.75)	5	2.9	1.75 (0.57-4.09)
Leukaemia - lymphoid (C91)	13	5.8	2.27 (1.21-3.89)	19	9.9	1.91 (1.15-2.99)
Leukaemia - myeloid (C92)	7	3.7	1.91 (0.77-3.95)	4	7.2	0.56 (0.15-1.43)
Liver (C22)	2	2.7	0.73 (0.09-2.64)	8	10.8	0.74 (0.32-1.46)
Lung (C33-C34)	28	34.1	0.82 (0.54-1.19)	71	63.9	1.11 (0.87-1.40)
Lymphoma - Hodgkins (C81)	2	1.6	1.28 (0.15-4.62)	0	1.2	0.00 (0.00-3.16)
Lymphoma - non-Hodgkins (C82-C85)	22	22	1.00 (0.62-1.52)	17	17.2	0.99 (0.58-1.58)
Melanoma - malignant (C43)	5	2.6	1.94 (0.63-4.55)	9	4.3	2.10 (0.96-4.00)
Meninges - benign (D32-D33)	22	19.9	1.11 (0.69-1.69)	9	8.7	1.04 (0.47-1.97)
Multiple myeloma (C90)	14	8.4	1.68 (0.91-2.82)	6	8.2	0.73 (0.27-1.59)
Nasopharynx (C11)	1	0.4	2.71 (0.07-15.15)	0	0.4	0.00 (0.00-8.68)
Nervous system - other (C70)	2	0.2	8.29 (1.00-30.00)	1	0.2	4.40 (0.11-24.78)
Oesophageal (C15)	16	12.5	1.29 (0.73-2.10)	20	14.3	1.39 (0.85-2.15)
Ovary (C56)	12	8.7	1.38 (0.71-2.42)	6	7.9	0.76 (0.28-1.65)
Pancreas (C25)	3	5.5	0.54 (0.11-1.58)	13	18.3	0.71 (0.38-1.21)
Prostate (C61)	101	98.6	1.03 (0.83-1.26)	86	70.7	1.22 (0.97-1.50)
Rectum (C20-C21)	34	37.7	0.90 (0.62-1.26)	19	18	1.05 (0.63-1.65)
Salivary gland (C07-C08)	2	1.7	1.20 (0.14-4.33)	2	1	1.98 (0.24-7.18)
Skin - other (C44)	310	323.5	0.95 (0.84-1.07)	109	111.9	0.97 (0.80-1.18)
Stomach (C16)	10	14.3	0.70 (0.33-1.29)	13	16.5	0.79 (0.42-1.35)
Testis (C62)	2	0.6	3.30 (0.4-11.94)	0	0.2	0.00 (0.00-15.34)
Thyroid (C73)	1	2.8	0.36 (0.01-2.02)	1	1.1	0.87 (0.02-4.87)
Uterus - body of (C54)	17	17	1.00 (0.58-1.61)	7	10.6	0.66 (0.26-1.36)

¹ The reference cohort comprised people who were coded in the HES dataset with the following conditions or operations, using Office of Population, Censuses and Surveys (OPCS) code edition 4 for operations and ICD10 code for diagnoses: adenoidectomy (OPCS4 E20), dilation and curettage (Q10.3+Q11.4), tonsillectomy (F34+F36), appendectomy (H01-H03), cataract (ICD 10 H25), squint (H49-H51), otitis externa/media (H60-H67), varicose veins (I83), haemorrhoids (I84), deflected septum, nasal polyp (J33+J34.2), inguinal hernia (K40), gall bladder disease (K80), in-growing toenail and other diseases of nail (L60), sebaceous cyst (L72.1), bunion (M20.1), contraceptive management (Z30). All comparisons with thereference cohort were adjusted for age in

315 five-year groups, sex, year of first admission, region of residence and quintile of the Index of Multiple Deprivation
316 (a standard UK measure of socio-economic status).
317
318 ² RRs were calculated using the formula O^{CAN}/E^{CAN} divided by O^{REF}/E^{REF} , where O and E are the observed and
319 expected numbers of BP in the cancer and reference cohort, respectively.
320