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ORIGINAL ARTICLE

Risk of solid malignancies in bullous pemphigoid: A large-scale population-based cohort study

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ABSTRACT

The association of bullous pemphigoid (BP) with solid malignancies (SM) is a matter of controversy, as previous studies produced inconclusive findings. The aim of this study was to assess the risk of SM among patients with BP and to evaluate whether a history of SM predisposes individuals to develop subsequent BP. A population-based cohort study was performed comparing BP patients (*n* = 3924) with age-, sex- and race-matched control subjects (*n* = 19 280) with regard to incident cases of SM. Adjusted hazard ratios (HR) and adjusted odds ratios (OR) were estimated by Cox regression and logistic regression, respectively. The incidence of SM was 13.4 (95% confidence interval [CI], 11.6–15.3) and 14.3 (95% CI, 13.5–15.1) per 1000 person-years among patients with BP and controls, respectively. BP was not associated with an increased risk of SM (adjusted HR, 0.90; 95% CI, 0.77–1.05). Additionally, a history of SM was not related to the risk of subsequent BP (adjusted OR, 1.00; 95% CI, 0.90–1.10). In a stratified analysis, patients with BP had an increased risk of uterine cancer (adjusted HR, 2.56; 95% CI, 1.39–4.72) unlike the 18 remaining analyzed types of SM. Relative to BP patients without SM, those with BP and SM were older, had a male predominance, a higher prevalence of smoking, a higher burden of comorbidities and comparable survival rates. Although patients with BP do not experience an overall increased risk of developing SM, they are more likely to have uterine cancer. Our findings argue against routine extended cancer screening for patients with incident BP, but raise the awareness of uterine cancer among females with BP.

Key words: **bullous pemphigoid, BP, cohort, risk, solid malignancy.**

INTRODUCTION

The burden of solid malignancies (SM) amongst patients with bullous pemphigoid (BP) has been the focus of considerable controversy. Studies that investigated this comorbidity have been inconclusive and inconsistent in their results. While an association between BP and SM was confirmed by some studies,[1,2] it was refuted by others,[3–6] thus leaving a confusing gap in the current published work. Additionally, the majority of studies investigating this topic were hindered either by methodological drawbacks, small sample size or both. Delineating the real comorbidity of BP with SM bears a substantial clinical implication as it may shed light on the need for cancer screening and may decisively affect the prognosis of patients.

The aim of the current study is to answer the question of whether patients with BP are at increased risk of developing SM. We additionally aimed to evaluate the prevalence of pre-existing SM among patients with BP. A granular analysis investigating the association between BP and 19 different types of SM was also performed, whereas our last end-point was to elucidate the clinical and epidemiological features of patients with BP and coexistent SM.

METHODS

Study design and dataset

The current study was performed to investigate the bidirectional association between BP and SM using a large study population of patients with BP. To delineate the risk of developing SM during the course of BP, a retrospective cohort study design was adopted to follow patients with BP with regard to the incidence of new-onset SM. A case–control study design was adopted to outline the prevalence of pre-existing SM in patients with subsequent BP.

The computerized dataset of Clalit Health Services (CHS) was the origin of the current study. CHS is the largest health-care maintenance organization in Israel, providing a wide array of private and public health-care services for 4 540 768

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enrollees as of October 2018. The different characteristics of the utilized dataset are detailed in other publications.[7,8]

Study population and definition of the main variables

The dataset of CHS was systematically checked for incident cases with a diagnostic code of BP between the years 2002 and 2019. Patients were eventually defined as eligible for inclusion only if one of the following criteria was met: (i) documented diagnosis of BP registered at least twice by a board-certified dermatologist; or (ii) diagnosis of BP in discharge letters of patients admitted to dermatological wards. We additionally recruited a control group including up to five enrollees lacking a diagnosis of BP per each case of BP. Controls were matched based on sex, age and race.

The diagnosis of each of the SM was based on its documentation in the cancer registry of the CHS. This registry is cross-linked with the National Cancer Registry and undergoes continuous updates and logarithmic checks. The SM variable was defined as the occurrence of any of the 19 SM available in the cancer registry of CHS. In those having more than one isolated SM, the date of the first cancer was considered as the event time.

Covariates and sensitivity analyses

To substantiate the validity of our findings, we performed a sensitivity analysis alongside the general analysis. This sensitivity analysis included only patients with BP who were prescribed "BP-related medications": systemic or topical corticosteroids for more than 6 months, as well as one of the adjuvant immunosuppressive or immunomodulatory agents (azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, dapsone, doxycycline, rituximab, plasmapheresis, i.v. immunoglobulins). This sensitivity analysis aimed to increase the reliability of the diagnosis of BP.

Outcome measures were adjusted for the Charlson Comorbidity Index, an epidemiological tool estimating the degree and severity of comorbid conditions of each study participant. This index is widely utilized in epidemiological studies and was evidenced to reliably predict mortality.[9] To avoid bias, we used a modified version of the score after dismissing the malignant component of this scoring system. Outcome measures were additionally adjusted for immunosuppressants owing to their carcinogenic effect.[10]

Statistical analysis

The comparison of different variables between cases and controls was performed using the χ^2-test and Student's *t*-test for categorical and continuous variables, respectively. In the cohort study design, incidence rates of SM were calculated for both BP patients and controls and expressed as the number of events per 1000 person-years. Hazard ratios (HR) for the risk of incident SM were obtained by the use of the Cox regression model. Differences in the cumulative survival of BP patients with and without SM were evaluated using a stratified log–rank test.

In the case–control study design, unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to compare cases and controls with regard to the presence of a pre-existing SM. The association was calculated based on individuals who developed BP after the diagnosis of SM as a temporal relationship exists between exposure and outcome in case–control studies. In the last section aiming to evaluate the epidemiological and clinical features of patients with BP and SM, all patients with both diagnoses were included regardless of the sequence of their appearance. Two-tailed *P*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 25 (IBM, Armonk, NY, USA).

RESULTS

Characteristics of the study population

The current study encompassed 23 204 participants, of whom 3924 were patients with BP and 19 280 were age-, sex and race-matched control subjects. The mean (standard deviation) age at the diagnosis of patients was 76.7 years (14.3), 2257 (57.5%) patients were female and 3752 (95.6%) patients were of Jewish race. The demographic and clinical features of patients with BP and controls are detailed in Table 1.

Table 1. Descriptive characteristics of the study population

Characteristic	Patients with bullous pemphigoid (*n* = 3924)	Controls (*n* = 19 280)	*P*
Age, years			
Mean (SD)	76.7 (14.3)	76.3 (14.3)	0.904
Median (range)	79.9 (0.4-104.4)	79.5 (0.7-103.8)	
Male sex, *n* (%)	1667 (42.5%)	8168 (42.4%)	0.908
Race, *n* (%)*			
Jewish	3752 (95.6%)	18 397 (95.4%)	0.584
Arabic	171 (4.4%)	868 (4.5%)	
BMI, mg/kg^2			
Mean (SD)	27.9 (6.1)	27.9 (8.4)	1.000
Smoking, *n* (%)	1148 (29.3%)	5771 (29.9%)	0.454
Charlson Comorbidity Index score			
Mean score (SD)	3.4 (2.4)	2.9 (2.3)	**<0.001**
None (0)	468 (11.9%)	3376 (17.5%)	**<0.001**
Moderate (1-2)	1113 (28.4%)	6177 (32.0%)	**<0.001**
Severe (≥3)	2343 (59.7%)	9727 (50.5%)	**<0.001**

*This variable was not available for all patientsBold text indicates statistical significance. BMI, body mass index; BP, bullous pemphigoid; SD, standard deviation.

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Table 2. Risk of solid malignancies among patients with bullous pemphigoid (retrospective cohort study design)

	BP	Controls
Follow-up time, PY	15 724.1	92 454.5
Median follow-up time, years (range)	3.4 (0.0–17.6)	4.6 (0.0–17.8)
No. of events	210	1321
Incidence rate/1000 PY (95% CI)	13.4 (11.6–15.3)	14.3 (13.5–15.1)
Crude HR (95% CI)	0.91 (0.78–1.05)	Reference
Male-specific crude HR (95% CI)	0.85 (0.68–1.06)	Reference
Female-specific crude HR (95% CI)	0.97 (0.79–1.18)	Reference
Sensitivity analysis crude HR (95% CI)[†]	0.87 (0.75–1.02)	Reference
Adjusted HR (95% CI)[‡]	0.92 (0.79–1.07)	Reference
Adjusted HR (95% CI)[§]	0.88 (0.73–1.04)	Reference

[†]Including only cases managed by BP-related medications.
[‡]Multivariate logistic regression model adjusting for age, sex and race.
[§]Multivariate logistic regression model adjusting for age, sex, race, comorbidities, smoking, alcohol consumption, body mass index and immunosuppressants. BP, bullous pemphigoid; CI, confidence interval; HR, hazard ratio; PY, person-years.

Risk of developing SM among patients with BP (retrospective cohort study design)

The overall incidence rate of SM was 13.4 (95% CI, 11.6–15.3) and 14.3 (95% CI, 13.5–15.1) per 1000 person-years among patients with BP and controls, respectively (Table 2).

The overall risk of developing incident SM was not significantly increased among patients with BP, neither in the whole study population (HR, 0.91; 95% CI, 0.78–1.05) nor among males (HR, 0.85; 95% CI, 0.68–1.06) nor females (HR, 0.97; 95% CI, 0.79–1.18). The comparable risk of SM persisted also following a sensitivity analysis, which included only BP patients managed by BP-related medications (HR, 0.87; 95% CI, 0.75–1.02) as well as the following adjustment for putative confounders (adjusted HR, 0.90 [95% CI, 0.77–1.05] and 0.88 [95% CI, 0.73–1.04]; Table 2).

Odds of BP in those with a preceding diagnosis of SM (case–control study design)

The prevalence of pre-existing SM was comparable between patients with BP and control individuals (14.9% vs 14.5%, respectively; OR, 1.04; 95% CI, 0.94–1.15; $P = 0.469$). Stratified analyses revealed no statistically significant association between pre-existing SM and subsequent BP in different age groups, both sexes and both main racial groups in Israel (Table 3). When the association was stratified in accordance with the latency between the appearance of SM and the later development of BP, significantly increased odds of BP appeared only between 2 and 5 years following the diagnosis of SM (OR, 1.23; 95% CI, 11.03–1.47; Table 3).

In a sensitivity analysis including only cases managed by BP-related medications, SM was not associated with the development of BP (OR, 0.97; 95% CI, 0.87–1.07). The association was not meaningfully altered after adjusting for demographic variables (adjusted OR, 1.01; 95% CI, 0.91–1.12) as well as for demographic variables alongside comorbidities, smoking, alcohol consumption, body mass index and intake of immunosuppressants (adjusted OR, 1.02; 95% CI, 0.89–1.12).

Association between BP and different types of SM

We then assessed the bidirectional association between BP and 19 different types of SM (Table 4). Female patients with BP were found to be at an independently increased risk of developing uterine cancer (adjusted HR, 2.56; 95% CI, 1.39–4.72). Interestingly, patients with BP did not experience an increased risk of developing any of the remaining 18 SM.

Although pre-existing pharyngeal cancer showed an increased prevalence among BP patients in univariate analysis (OR, 1.73; 95% CI, 1.04–2.89), this association lost its statistical significance after adjusting for putative confounders (adjusted OR, 1.57; 95% CI, 0.93–2.66). Correspondingly, no association was evidenced between any of the remaining types of SM and the subsequent development of BP (Table 4).

Characteristics of patients with coexistent BP and SM

The eventual end-point of the current study was to compare patients with concomitant BP and SM ($n = 765$) relative to the remaining patients with SM ($n = 3159$; Table S1). Patients in the former subgroup were found to be older at the onset of BP, had a higher prevalence of males and smokers, have a higher burden of comorbidities and higher frequency of programmed death 1/programmed death ligand 1-associated BP (Table S1).

We additionally compared the survival rates of the two subgroups and found that the risk of all-cause mortality was comparable between BP patients with and without SM (HR, 1.09; 95% CI, 0.98–1.21; $P = 0.104$; Fig. 1).

DISCUSSION

The current population-based study shows that the diagnosis of BP does not impose an overall elevated risk of developing subsequent SM, and that patients with BP do not have an overall increased prevalence of pre-existing SM. Of all the analyzed SM types, patients with BP had only an increased risk of developing uterine cancer. Patients with BP and coexistent SM

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Table 3. Prevalence of pre-existing solid malignancy, stratified by age, sex, race and latency from the diagnosis of solid malignancy (case–control study design)

Subgroup	SM in patients with BP, *n* (%)†	SM in controls, *n* (%)†	OR (95% CI)	Univariate *P*
All	555 (14.9)	2611 (14.5)	1.04 (0.94–1.15)	0.469
Age, years				
<70	59 (7.3)	262 (6.3)	1.17 (0.88–1.57)	0.283
71–80	167 (16.1)	752 (14.8)	1.11 (0.92–1.33)	0.282
≥80	329 (17.6)	1587 (18.2)	0.96 (0.84–1.09)	0.529
Sex				
Male	280 (17.8)	1240 (16.5)	1.10 (0.95–1279)	0.195
Female	275 (12.8)	1361 (13.0)	0.98 (0.85–1.13)	0.792
Race				
Jewish	547 (15.4)	2541 (14.8)	1.05 (0.95–1.16)	0.388
Arabic	8 (4.9)	60 (7.2)	0.66 (0.31–1.41)	0.278
Latency after the diagnosis of SM				
0–1 year	38 (1.00)	158 (0.9)	1.17 (0.82–1.66)	0.401
2–5 years	163 (4.4)	645 (3.6)	**1.23 (1.03–1.47)**	**0.020**
6–10 years	141 (3.8)	680 (3.8)	1.00 (0.83–1.21)	0.977
≥10 years	213 (5.7)	1118 (6.2)	0.92 (0.79–1.07)	0.257

Bold text indicates statistical significance.
†The prevalence of SM in cases when SM preceded BP (in cases) or preceded recruitment (in controls). BP, bullous pemphigoid; CI, confidence interval; OR, odds ratio; SM, solid malignancy.

were older, had a higher frequency of males and smokers, as well as a higher comorbidity burden.

Inconsistency of the association between BP and SM in the current published work

The association between BP and SM was investigated in several controlled observational studies. However, they provided inconsistent findings and were hampered by methodological flaws that interfered with their external validity. Two cross-sectional studies counting 50 and 84 patients with BP demonstrated a significant association with BP and SM with OR of 3.6 (95% CI, 1.2–10.7) and 2.9 (95% CI, 1.2–7.3), respectively.[1,2] Conversely, another cross-sectional study encompassing 73 patients with BP found no significant association between these conditions (OR, 0.7; 95% CI, 0.3–1.7).[4] Apart from their small sample size and low statistical power, these studies were cross-sectional, and therefore unable to identify the temporal relationship between the diagnoses of interest and to draw any conclusion about risk and causality.[11] These three studies were synthesized in a meta-analysis generating an insignificant pooled OR of 1.9 (95% CI, 0.7–5.5).[12] This finding was reinforced by a cross-sectional study of Schulze *et al*.,[3] declaring that no significant association existed between BP and SM, but without reporting the precise outcome measures.

In their case–control study of 89 patients with BP, Jedlickova *et al*.[5] found that the prevalence rate of pre-existing SM was comparable between patients with BP and controls (OR, 1.3; 95% CI, 0.5–3.4). The latter was hampered by small sample size and susceptibility to selection bias owing to the single-center setting. One retrospective cohort study followed a large cohort of patients with BP ($n = 4720$) and found no increased risk of developing any subsequent SM. The same study followed a large population of patients with different SM and found that an overall history of SM does not predispose individuals to develop BP, except larynx (relative risk [RR], 2.2; 95% CI, 1.2–3.8) and kidney (RR, 2.2; 95% CI, 1.5–3.2) cancers.[6] It is noteworthy that other studies investigated the association between BP and malignant condition, but lacked differentiation between solid and hematological malignancies.[12,13]

Interpretations and implication of the study findings

We showed that patients with BP do not experience an overall elevated risk of developing SM, in accordance with the single population-based cohort study investigating the risk of SM during the course of BP.[6] By the case–control design, we additionally showed that the overall prevalence of pre-existing SM was comparable between patients with BP and controls. The latter held truth in the multivariate analysis of all 19 analyzed SM. Correspondingly, the prevalence of pre-existing SM was comparable between BP patients and controls in the only case–control study exploring this association.[5]

Our finding showed that a diagnosis of BP places patients at an increased risk of developing uterine cancer. This lends weight to previous anecdotal case reports and case series describing the coexistence of BP and uterine cancer.[14–16] This epidemiological finding may be substantiated by an experimental study showing increased immunoreactivity and mRNA synthesis of BP180 (the main autoantigen implicated in the pathogenesis of BP) in cells of endometrial adenocarcinomas as well as intensified expression of BP180 in hyperplastic endometrium. The aforementioned alteration in the expression

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Table 4. Association between bullous pemphigoid and different solid malignancies

	Odds of having BP after SM (case–control design)					Risk of SM after the diagnosis of BP (cohort study design)				
	No. of cases (among BP, among controls)	OR (95% CI)	*P*	Adjusted OR (95% CI)[a]	*P*	No. of cases (among BP, among controls)	HR (95% CI)	*P*	Adjusted HR (95% CI)[†]	*P*
Breast cancer[‡]	(141, 758)	0.91 (0.75–1.08)	0.238	0.89 (0.73–1.07)	0.212	(37, 205)	1.02 (0.71–1.46)	0.908	1.04 (0.72–1.48)	0.854
Bone cancer	(5, 17)	1.42 (0.53–3.86)	0.486	1.51 (0.98–1.05)	0.423	(2, 13)	0.93 (0.21–4.10)	0.918	1.07 (0.24–4.83)	0.935
Brain and CNS cancer	(8, 23)	1.68 (0.75–3.77)	0.200	1.79 (0.80–4.02)	0.159	(3, 28)	0.64 (0.19–2.10)	0.461	0.69 (0.21–2.29)	0.546
Cervix cancer[‡]	(5, 27)	0.90 (0.35–2.33)	0.820	0.71 (0.25–2.03)	0.522	(3, 13)	1.58 (0.44–5.67)	0.482	1.53 (0.42–5.50)	0.519
Colorectal cancer	(127, 625)	0.98 (0.81–1.19)	0.854	0.89 (0.73–1.09)	0.275	(36, 268)	0.81 (0.57–1.14)	0.229	0.82 (0.57–1.16)	0.260
Esophageal cancer	(4, 19)	1.02 (0.35–2.99)	0.974	1.09 (0.37–3.27)	0.871	(2, 12)	1.11 (0.25–5.00)	0.894	1.09 (0.24–4.94)	0.911
Kidney cancer	(33, 120)	1.33 (0.91–1.96)	0.144	1.24 (0.84–1.84)	0.275	(15, 76)	0.98 (0.53–1.80)	0.940	0.97 (0.53–1.80)	0.928
Larynx cancer	(10, 57)	0.85 (0.43–1.66)	0.630	0.86 (0.44–1.70)	0.667	(3, 18)	0.98 (0.29–3.34)	0.978	0.98 (0.29–3.38)	0.980
Liver and bile duct cancer	(5, 31)	0.78 (0.30–2.01)	0.605	0.75 (0.29–1.94)	0.748	(9, 66)	0.79 (0.40–1.59)	0.514	0.68 (0.33–1.42)	0.305
Lung cancer	(30, 137)	1.06 (0.71–1.58)	0.776	1.05 (0.70–1.57)	0.822	(22, 163)	0.73 (0.46–1.17)	0.191	0.75 (0.47–1.20)	0.227
Ovarian cancer	(13, 44)	1.43 (0.77–2.66)	0.255	1.52 (0.81–2.85)	0.188	(3, 16)	1.09 (0.32–3.72)	0.891	1.15 (0.33–3.99)	0.821
Pancreatic cancer	(5, 45)	0.54 (0.21–1.35)	0.180	0.50 (0.20–2.27)	0.147	(10, 86)	0.69 (0.36–1.33)	0.265	0.69 (0.36–1.33)	0.270
Pharynx cancer	(20, 56)	**1.73 (1.04–2.89)**	**0.033**	1.57 (0.93–2.66)	0.091	(9, 37)	1.50 (0.72–3.13)	0.276	1.47 (0.70–3.07)	0.304
Prostate cancer[§]	(119, 523)	1.10 (0.90–1.35)	0.340	1.06 (0.86–1.31)	0.596	(27, 156)	0.97 (0.64–1.48)	0.891	0.97 (0.63–1.49)	0.872
Stomach cancer	(16, 74)	1.05 (0.61–1.80)	0.871	0.99 (0.57–1.74)	0.982	(6, 61)	0.61 (0.26–1.41)	0.249	0.54 (0.22–1.36)	0.192
Sarcoma and soft tissue cancer	(14, 69)	0.98 (0.55–1.74)	0.948	0.90 (0.50–1.64)	0.736	(9, 30)	1.76 (0.83–3.73)	0.138	1.65 (0.78–3.52)	0.192
Thyroid cancer	(19, 94)	0.98 (0.60–1.60)	0.927	1.04 (0.63–1.71)	0.875	(3, 12)	0.97 (0.22–4.32)	0.965	1.05 (0.23–4.76)	0.949
Uterine cancer[‡]	(31, 105)	1.43 (0.96–2.14)	0.079	1.36 (0.89–2.06)	0.149	(15, 34)	**2.66 (1.44–4.90)**	**0.002**	**2.56 (1.39–4.72)**	**0.003**
Urinary bladder cancer	(64, 326)	0.95 (0.72–1.24)	0.701	0.91 (0.69–1.20)	0.506	(20, 155)	0.72 (0.46–1.20)	0.220	0.72 (0.45–1.16)	0.178

Bold text indicates statistical significance.
BP, bullous pemphigoid; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; NA, not applicable; OR, odds ratio; SM, solid malignancy.
[a]Multivariate logistic regression model adjusting for age, sex, ethnicity, comorbidities, and immunosuppressants.
[†]Multivariate logistic regression model adjusting for age, sex, race, comorbidities and immunosuppressants.
[‡]Calculated among females.
[§]Calculated among males.

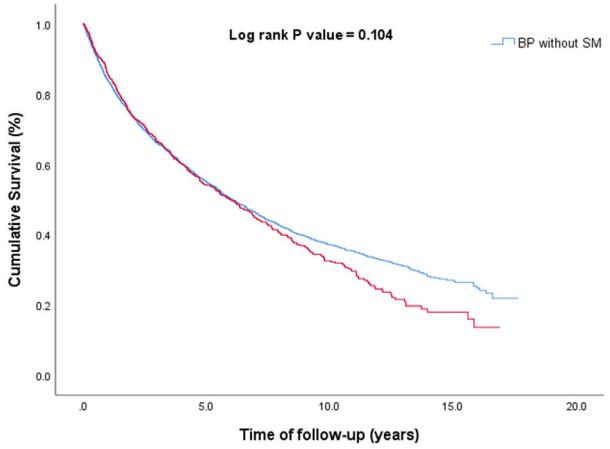

Figure 1. Kaplan–Meier curves representing differences in the cumulative survival between bullous pemphigoid patients with (red) and without (blue) solid malignancy.

of BP180 in endometrial adenocarcinomas may signify its role in the neoplastic growth of this malignancy.[17] Altogether, it may be alleged that a cross-reactive immunoresponse between epidermal and uterine isoforms of BP180 may lead to persistent inflammation (possibly subclinical) in the uterine tissue, which may eventually contribute to the development of carcinogenesis and neoplasia,[18] via inducing proneoplastic mutations, resistance to apoptosis and environmental changes such as stimulation of angiogenesis.[18–20] Much of the comprehension of the link between chronic inflammation and cancer was acquired through the association between chronic inflammatory bowel diseases and the increased risk of colon carcinoma.[21] Still, patients with coexistent BP and uterine cancer should be further investigated to confirm or refute this hypothesis. The higher age of patients with BP and coexistent SM reflects the increased risk of malignancies with aging and accords with the increasing trend for internal malignancies with aging among Japanese patients with BP.[16]

Strengths and limitations

The current large-scale population-based study investigated a controversial topic with inconsistent conclusions drawn from previous studies exploring it. The large sample size grants sufficient power to exclude chance as the basis of the observations and overcomes the main hindrances of the previous studies. The population-based setting enabled the inclusion of patients managed at all health-care levels, thus disproving the presence of meaningful selection bias.

The study has some limitations to be acknowledged, like the lack of data concerning the immunoserological and morphological features of BP, as well as the precise histological type of each cancer. However, the diagnoses of both BP and malignancies in our study are of reliable validity because the diagnosis of BP relied only on documentation by certified dermatologists and dermatological wards, and because the chronic diseases registry of CHS is cross-linked with the Israel National Cancer Registry. The probability of residual confounding could not be thoroughly refuted despite the multivariable logistic regression model.

In conclusion, the current population-based study disclosed that patients with BP do not have an increased overall risk of SM. Compared with matched control individuals, patients with BP had a similar prevalence of pre-existing SM. In a granular analysis stratifying by different types of SM, a diagnosis of BP was associated with a 2.6-fold increased risk of subsequent uterine cancer, but with none of the remaining types of SM. Our findings argue against and refute the approach of performing comprehensive cancer screening in patients newly diagnosed with BP. Nonetheless, awareness may be raised with respect to the risk of uterine cancer in females with BP.

CONFLICT OF INTEREST: A. D. C. served as an advisor, investigator or speaker for Abbvie, BI, Dexcel Pharma, Janssen, Novartis, Perrigo, Pfizer and Rafa.

REFERENCES

1 Venning VA, Wojnarowska F. The association of bullous pemphigoid and malignant disease: a case control study. *Br J Dermatol* 2006; **123**(4): 439–445.
2 Caccavale S. The association of bullous pemphigoid and malignancy: A case control study. *G Ital Dermatol Venereol* 2015; **150**(6): 764–765.
3 Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. *J Invest Dermatol* [Internet]. 2015;**135**(10):1445–1447.
4 Stone SP, Schroeter AL. Bullous pemphigoid and associated malignant neoplasms. *Arch Dermatol* 1975; **111**(8): 991–994.
5 Jedlickova H, Hlubinka M, Pavlik T, Semradova V, Budinska E, Vlasin Z. Bullous pemphigoid and internal diseases - A case-control study. *Eur J Dermatology*. 2010; **20**(1): 96–101.
6 Ong E, Goldacre R, Hoang U, Sinclair R, Goldacre M. Associations between bullous pemphigoid and primary malignant cancers: an English national record linkage study, 1999–2011. *Arch Dermatol Res*. 2014; **306**(1): 75–80.
7 Kridin K, Ludwig RJ, Tzur Bitan D, Kridin M, Damiani G, Cohen AD. Is gout associated with pyoderma gangrenosum? A population-based case-control study. *J Clin Med*. 2020; **9**(6): 1626. https://orcid.org/10.3390/jcm9061626
8 Kridin K, Zelber-Sagi S, Comaneshter D, Cohen AD. Coexistent solid malignancies in pemphigus. *JAMA Dermatol* 2018; **154**:435-440.
9 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**(5): 373–383.
10 Gallagher MP, Kelly PJ, Jardine M *et al*. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *J Am Soc Nephrol* 2010; **21**(5): 852–858.
11 Höfler M. The Bradford Hill considerations on causality: a counterfactual perspective. *Emerg Themes Epidemiol* 2005; **2**: 11.
12 Atzmony L, Mimouni I, Reiter O *et al*. Association of bullous pemphigoid with malignancy: a systematic review and meta-analysis. *J Am Acad Dermatol* 2017; **77**(4): 691–699.
13 Chen CT, Hu HY, Chang YT, Li CP, Wu CY. Cancer is not a risk factor for bullous pemphigoid: 10-year population-based cohort study. *Br J Dermatol* 2019; **180**(3): 553–558.
14 Toi T, Kuwasako Y, Nakajima I *et al*. Successful combined spinal-epidural anesthesia for the endometrial cancer patient with merged

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bullous pemphigoid - Report of case. *J Showa Med Assoc* 2007; **67**: 217–220.
15 Isohashi F, Konishi K, Umegaki N, Tanei T, Koizumi M, Yoshioka Y. A case of bullous pemphigoid exacerbated by irradiation after breast conservative radiotherapy. *Jpn J Clin Oncol* 2011; **41**(6): 811–813.
16 Ogawa H, Sakuma M, Morioka S *et al*. The incidence of internal malignancies in pemphigus and bullous pemphigoid in Japan. *J Dermatol Sci* 1995; **9**(2): 136–141.
17 Määttä M, Salo S, Tasanen K *et al*. Distribution of basement membrane anchoring molecules in normal and transformed endometrium: Altered expression of laminin γ2 chain and collagen type XVII in endometrial adenocarcinomas. *J Mol Histol* 2004; **35**(8-9): 715–722.
18 Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncol (willist Park NY)*. 2002; **16**(2):217–226, 229; discussion 230–2.
19 Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; **420** (6917): 860–867.
20 Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**(6): 883–899.
21 Ekbom A, Helmick C, Zack M, Adami H-O. Ulcerative colitis and colorectal cancer. *N Engl J Med* 1990; **323**(18): 1228–1233.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison between patients with coexistent bullous pemphigoid and solid malignancies relative to the remaining patients with bullous pemphigoid

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