Appendix S3). A selection bias was suspected in many RCTs (57/70) (row 2, Appendix S3). High risk of attrition bias and reporting bias was evident in 19 of 70 and 20 of 70 RCTs, respectively (rows 5 and 6, Appendix S3). Thirty-five RCTs were published since the first CONSORT (Consolidated Standards of Reporting Trials) statement was released (1996)[5]; among these, 12 had a high or uncertain risk of reporting bias. AGW clearance was assessed from immediately after treatment (mainly for provider-administered therapies) up to 4 months later, depending on the study. Recurrence was occasionally assessed (15/70 RCTs) 1-12 months after clearance.

The following should be considered in future RCTs. Participants and physicians should be systematically blinded to the allocated intervention, and both AGW clearance and recurrence should be assessed at fixed time points (a consensus is lacking on this point) by an independent expert unaware of the allocated intervention. Proper randomization procedures should be strictly followed. The CONSORT statement must imperatively be employed. Systematic information on previous therapies and on AGW location and characteristics should be provided to enable efficacy analyses. The unit of analysis must always be the patient, as the primary goal is full recovery. Split studies should be avoided for statistical reasons but also because of the risk of performance bias. In future RCTs, the percentage of AGW recurrence, which is an important yet often neglected outcome, should also be evaluated. Nevertheless, RCT assessment of recurrence raises important methodologic problems, including a high rate of loss to follow-up and recontamination.

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Association between prurigo nodularis and malignancy in middle-aged adults

To the Editor: Prurigo nodularis (PN) is an extremely pruritic, inflammatory skin disease associated with multiple underlying comorbidities.[1] Case reports have noted an association between PN and malignancies, including lymphoma[2,3] and solid organ tumors.[4] The goal of this cross-sectional study was to evaluate an association between PN and a variety of malignancies in a diverse patient population.

Institutional review board approval was waived for this study because only anonymous aggregate-level data were used. The study population consisted of 695 patients aged 40-69 years who presented to the Johns Hopkins Health System during 2013-2017

Table I. Demographic characteristics of the PN group and comparison group without PN

Characteristic	PN group, n = 695, %	Control group, n = 2,454,685, %
Sex		
Male	48.35	45.42
Female	51.65	54.58
Race		
White, Caucasian	41.44	60.98
Black, African American	51.37	22.13
Asian	2.59	3.81
American Indian or Alaskan native	0.14	0.21
Native Hawaiian, other Pacific Islander	0.14	0.05
Other	4.32	6.31
Unknown	1.15	8.13
Declined to answer	0.14	0.21
Age, y		
40-49	25.61	32.85
50-59	44.93	36.34
60-69	29.46	30.80

In total, 695 patients aged 40-69 years who presented to Johns Hopkins Health System during April 2013-December 2017 with a visit diagnosis, billing diagnosis, or active problem list entry of PN were identified. The comparison population was 2,446,880 patients aged 40-69 years without a diagnosis of PN.
PN, Prurigo nodularis.

with a PN diagnosis. They were compared with 2,446,880 control patients also aged 40-69 years (Table I) because this age range is the peak for PN occurrence.[1] Patients with a diagnosed malignancy were identified within the PN and control groups, and odds ratios (ORs) were calculated. *P* values were calculated by using χ^2 statistics with 1 degree of freedom. A Bonferroni correction was applied (alpha = 0.002). For malignancies of the genital tracts, only patients of the relevant sex were included.

Of the 695 patients with PN, 124 had a concomitant diagnosis of malignancy during the study period (Fig 1, *A*). Patients with PN were >4 times more likely than controls to have a malignancy diagnosis (OR 4.54, 95% confidence interval [CI] 3.74-5.52). PN was significantly associated with cancers of the skin (OR 10.94, 95% CI 8.01-14.96), hematopoietic system (OR 5.41, 95% CI 3.39-8.64), and solid organs (OR 3.44, 95% CI 2.34-5.06) (Fig 1, *B*). Among the hematologic malignancies, PN was most strongly associated with primary cutaneous lymphoma (OR 24.82, 95% CI 7.96-77.46), multiple myeloma (OR 6.55, 95% CI 2.45-17.51), and non-Hodgkin lymphoma (OR 5.66, 95% CI 2.82-11.38). Among solid organ malignancies, PN was most strongly associated with cancers of the female genital organs (OR 11.00, 95% CI 4.90-24.68), gastrointestinal tract (OR 5.08, 95% CI 2.11-12.26), and lung (OR 4.63, 95% CI 1.92-11.16).

There are several limitations to this study. There might be a selection bias for the detection of dermatologic malignancies because PN patients are more likely to be under the care of dermatologists. Also, we cannot draw conclusions about the causal relationship between PN and malignancy from these data. However, case reports have shown that PN can improve with cancer treatment,[2-4] suggesting that PN might be downstream. In the case of hematologic malignancies, PN might be the result of inflammatory infiltration of the skin, leading to pruritus and excoriation. The mechanisms by which other malignancies predispose patients to PN remain unclear but might be related to systemic inflammatory states.

We conclude that PN might be associated with a wide variety of malignancies. The time course of the association and the risk-to-benefit ratio of cancer screening in this patient population requires further investigation, but cohort studies of generalized pruritus have suggested that the risk of cancer diagnosis is highest in the first 3 months after onset.[5] At minimum, clinicians caring for PN patients should be vigilant for signs or symptoms suggestive of malignancy and ensure that these patients receive all recommended age-appropriate cancer screening.

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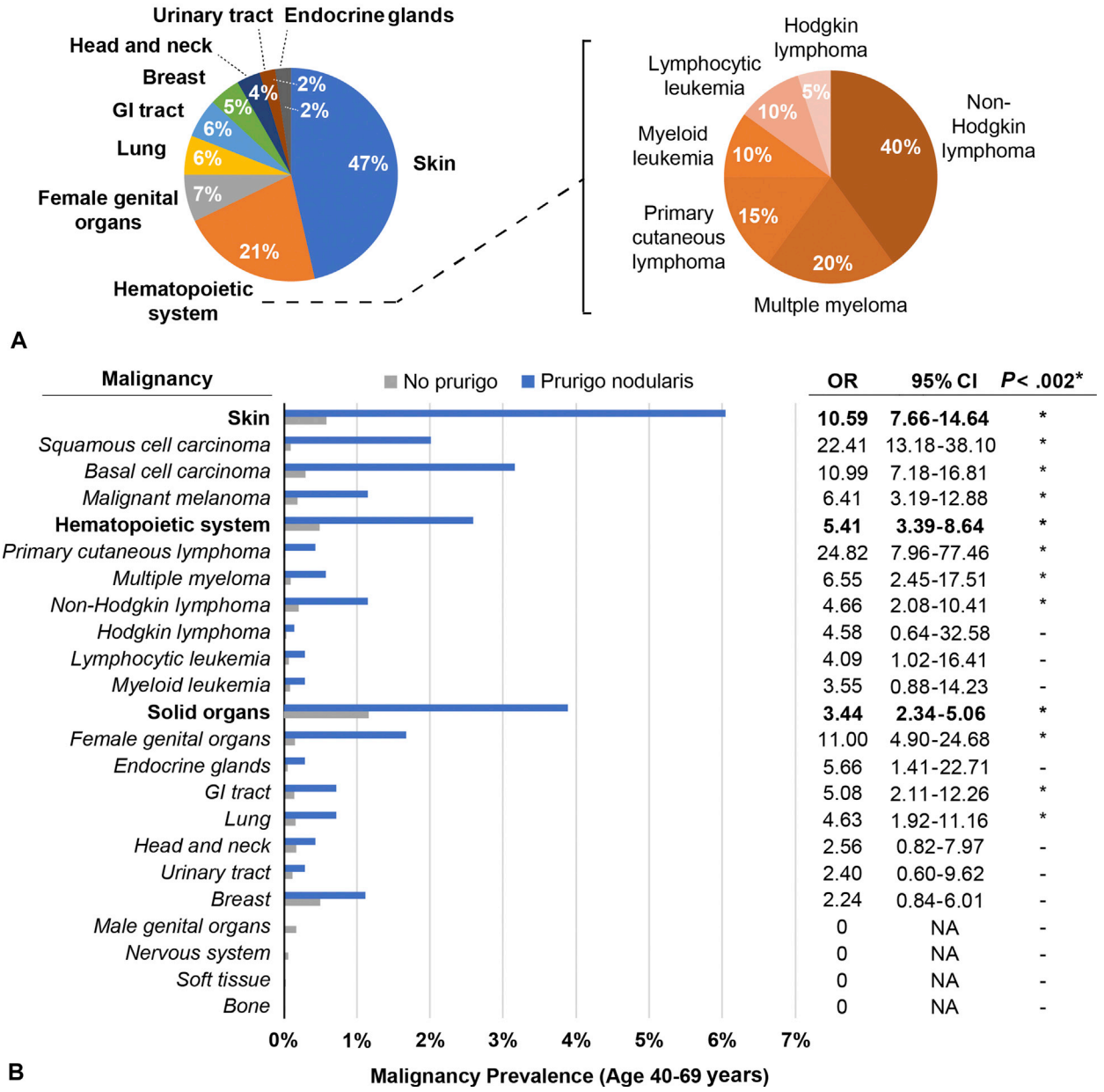

Fig 1. Malignancies in prurigo nodularis (PN) patients. **A**, Distribution of 124 malignancies diagnosed in PN patients during the 5-year study period, by anatomic origin. Hematopoietic system malignancies are further subdivided by disease entity. **B**, Prevalence of different malignancy categories in PN patients (*blue*) and patients without PN (*gray*) in the Johns Hopkins Health System population. ORs and 95% CIs for each malignancy type are tabulated on the right. Row section heads are indicated in bold. *$P < .002$ (χ^2 test). †Noncutaneous. *CI*, Confidence interval; *GI*, gastrointestinal; *NA*, not applicable; *OR*, odds ratio; *PN*, prurigo nodularis.

Reprints not available from the authors.

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Evaluation of preoperative quality of life in patients with nonmelanoma skin cancer

To the Editor: It is estimated that more than 4,000,000 adults were treated for nonmelanoma skin cancer (NMSC) between 2007 and 2011, with average annual treatment costs of approximately $4.8 billion in the US population.[1] The average number of adults treated annually for skin cancer in the US population increased from 3.4 million in 2002-2006 to 4.9 million in 2007-2011, with the average annual total cost for skin cancer increasing from $3.6 billion to $8.1 billion (an increase of 126.2%), demonstrating that the health and economic burden of skin cancer treatment is vastly increasing.[2] The aim of this study was to identify factors that predict lower quality of life (QOL) scores in patients undergoing Mohs micrographic surgery for NMSC.

The Skin Cancer Index (SCI), a 15-item validated QOL questionnaire, was administered to a prospective cohort of patients with NMSC at a 2-physician academic dermatologic surgery center. The SCI was used, as it is disease specific to NMSC and has been previously validated in a dermatologic surgery setting.[3] A 5-point response format was used to assess the extent to which each item described the feelings of the patient, with 1 meaning very much and 5 meaning not at all and a higher score indicating better QOL. Patients with diagnosed NMSC who were attending the Brigham and Women's Hospital Mohs and Dermatologic Surgery Center from March 2014 through March 2015 were eligible for participation in the study. A 2-sample *t* test with unequal variances and Welch's approximation was used to examine factors predictive of overall SCI score and scores on the social, emotional, and appearance subscales. Statistical analyses were performed by using Stata software (version 12.0, StataCorp, College Station, TX). The Partners Human Research Committee approved this study.

Table I summarizes the characteristics of the study cohort. A total of 389 patients were included in the study. Eleven patients declined to participate. In our overall analysis, independent predictors of lower overall SCI score were younger age ($P < .001$), female sex ($P < .001$), being employed ($P < .001$), and tumor location on the head and neck ($P < .01$) (Table II). Independent predictors of lower subscale scores were as follows: on the social subscale,

Table I. Baseline cohort characteristics

Variable	n	%
Total patients	389	
Mean age, y (SD)	66.5 (13.1)	
Age range, y	20-95	
Sex		
Male	197	50.6
Female	192	49.4
Race		
White	385	99.0
Other	4	1.0
Employment status		
Employed	195	50.1
Retired	175	45.0
Unemployed/unknown	19	4.9
Immunosuppression		
No	335	13.9
Yes	54	86.1
History of skin cancer		
No	156	40.1
Yes	233	59.9
Comorbidity*		
Hypertension	112	31.4
Diabetes	34	8.7
Hyperlipidemia	26	6.7
Type of skin cancer treated		
Basal cell carcinoma	247	63.5
Invasive squamous cell carcinoma	105	27.0
Squamous cell carcinoma in situ	15	3.9
Other	22	5.7
Location of skin cancer		
Head/neck (including ear/lip)	300	77.1
Trunk	21	5.4
Extremities	65	16.7
Genitalia	3	0.8
Mean tumor diameter, cm (SD)	1.42 (1.00)	
Mean postoperative area size, cm (SD)	2.68 (5.67)	
Median QOL score (IQR)†		
Overall Skin Cancer Index	81.9 (70.0-91.2)	
Emotional subscale	71.4 (53.6-85.7)	
Social subscale	95.0 (85.0-100.0)	
Appearance subscale	83.3 (58.3-100.0)	

IQR, Interquartile range; *QOL*, quality of life; *SD*, standard deviation.
*Less than 5% of patients had the following comorbidities: chronic obstructive pulmonary disease, stroke, breast cancer, prostate cancer, lymphoma, leukemia, colon cancer, lung cancer, depression, and ulcerative colitis.
†Each raw score was standardized by using the formula (raw score − 1) × (100/4).