**Methods**

***Study Design and Database***

We performed a retrospective population-based case-control study aiming to identify the risk of having subsequent PG following the diagnosis of UC. “The rare disease assumption” hypothesizes that estimates produced by case-control studies investigating rare diseases (defined as those with a prevalence rate <10%) approximates that produced by cohort studies [9]. Thus, the case-control study design utilized in the current study enables to evaluate the risk of PG in subjects with a history of UC.

The computerized dataset of Clalit Health Services (CHS) was the origin of the current study. CHS is the largest health care organization in Israel, providing healthcare services for approximately 4,400,000 enrollees. It provides a wide array of both public and private healthcare services. The computerized database of CHS is characterized by incessant real-time input from medical, administrative, and pharmaceutical operating systems. It was proven highly competent to enable the performance of epidemiological studies.

The chronic disease registry of CHS retrieves data from various sources, including from hospital and primary care reports, drug claims. These accumulated data is then manually cross-checked and validated by the primary care practitioner of each patient. This registry was considered as of vast reliability on the grounds of previous epidemiological studies [10].

The ethical committee of Ben-Gurion University approved the current study which was performed in accordance with the Declaration of Helsinki.

***Study Population and Covariates***

Between the years 2000 and 2018, we identified all individuals with diagnostic codes consistent with the diagnosis of PG. The inclusion of PG cases in this study was based on the following criteria: (i) a documented diagnosis of PG at least twice in the medical file as registered by a community board-certified dermatologist or (ii) documentation of a diagnosis of PG in hospital discharge letters from dermatological wards. Figure 1 illustrates selection of study population.

The diagnosis of UC was based on its registration in the chronic registry of CHS. To elaborate, it is based on the documentation of board-certified gastroenterologist, on the claims of UC-related drugs, and is eventually validated by the managing general practitioner.

The control group included up to 5 controls per patient, matched randomly by age, sex, and ethnicity. Age matching was based on the exact year of birth (1-year strata). The diagnosis date was used as an index date for the cases, and each matched control patient. Controls were ascertained to be alive and to contribute longitudinal data to the CHS dataset at their recruitment date.

 Outcome measures were adjusted for comorbid underlying diseases utilizing the Charlson comorbidity index, a validated epidemiological method of measuring and categorizing comorbidities. This index has been demonstrated to be reliable in forecasting mortality [11]. Smoking status was classified as a current smoker or never/past smoker.

***Statistical Analysis***

Baseline characteristics are described with means and standard deviations (SD)s for continuous variables, whereas percentages are used to represent categorical values. A comparison of the distribution of sociodemographic and clinical factors between patients with PG and controls was conducted using the χ2 test and *t* test, as indicated.

Logistic regression was used to calculate odds ratios (ORs) and 95% CIs to compare cases and control with respect to the presence of UC. The association was calculated based on individuals who developed PG following the diagnosis of UC in accordance with the presence of a temporal relationship between exposure and outcome in case-control studies. Two-tailed *p* values less than 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS software, version 25 (SPSS, Armonk, NY: IBM Corp).

A sensitivity analysis was performed to ensure that the observed association was not overestimated due to ascertainment bias. This analysis was based on repeating all calculations with an exclusion period of 2 years prior to the diagnosis of PG. Thus, all individuals given a diagnosis of UC in this period were omitted from all calculations.