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Association of Psoriasis With the Risk of Developing or Dying of Cancer A Systematic Review and Meta-analysis

Alex M. Trafford, MSc; Rosa Parisi, PhD; Evangelos Kontopantelis, PhD; Christopher E. M. Griffiths, MD; Darren M. Ashcroft, PhD

IMPORTANCE The risk of cancer developing in people with psoriasis has raised some concern, with little clarity regarding differentiation in risk according to psoriasis severity.

OBJECTIVE To conduct a systematic review and meta-analysis of observational studies on the risk of cancer incidence and mortality in people with psoriasis.

DATA SOURCES Six electronic databases (MEDLINE, Embase, MEDLINE in Process, Cochrane Central Register, Web of Science, and LILACS [Literatura Latino-Americana e do Caribe em Ciências da Saúde]) were searched from inception to November 15, 2017, for eligible studies.

STUDY SELECTION Cohort and case-control studies that provided estimates of the risk of cancer incidence or cancer mortality associated with psoriasis were included.

DATA EXTRACTION AND SYNTHESIS Data were extracted relating to study design, study population, and risk estimates. Study-specific estimates of the relative risk (RR) were combined using a random-effects model. Heterogeneity was quantified using the *I*² statistic. Data were analyzed from April 9, 2018, through February 22, 2019.

MAIN OUTCOMES AND MEASURES Pooled RR estimates for cancer incidence and cancer mortality for psoriasis cohorts compared with people without psoriasis.

RESULTS A total of 58 unique studies were included, with quality varying for the incidence and the mortality studies. Severe psoriasis (RR, 1.22; 95% CI, 1.08-1.39 [9 studies]) and all severities of psoriasis (RR, 1.18; 95% CI, 1.06-1.31 [7 studies]) were associated with an increased risk of cancer (overall), and associations were found for a range of site-specific cancers, including colon (RR, 1.18 [95% CI, 1.03-1.35]), colorectal (RR, 1.34 [95% CI, 1.06-1.70]), kidney (RR, 1.58 [95% CI, 1.11-2.24]), laryngeal (RR, 1.79 [95% CI, 1.06-3.01]), liver (RR, 1.83 [95% CI, 1.28-2.61]), lymphoma (RR, 1.40 [95% CI, 1.24-1.57]), non-Hodgkin lymphoma (RR, 1.28 [95% CI, 1.15-1.43]), keratinocyte cancers (RR, 1.71 [95% CI, 1.08-2.71]), esophageal (RR, 2.05 [95% CI, 1.04-4.07]), oral cavity (RR, 2.80 [95% CI, 1.99-3.93]), and pancreatic (RR, 1.41 [95% CI, 1.16-1.73]). Overall cancer mortality risk was higher in patients with severe psoriasis (RR, 1.22; 95% CI, 1.08-1.38 [4 studies]). Specifically, liver (RR, 1.43 [95% CI, 1.09-1.88]), esophageal (RR, 2.53 [95% CI, 1.87-3.41]), and pancreatic (RR, 1.31 [95% CI, 1.02-1.69]) cancer mortality were found to be elevated in those with severe psoriasis. The heterogeneity of estimates was often very high despite stratification. Marked attenuation of risk was found in those studies that adjusted estimates for smoking, alcohol consumption, and obesity.

CONCLUSIONS AND RELEVANCE In this study, people with psoriasis appeared to have an increased risk of cancer incidence and cancer-related mortality involving a range of site-specific cancers. Future research examining specific lifestyle factors, treatments, and the inflammatory processes that contribute to psoriasis may help provide additional information on the underlying mechanisms for the apparent increased cancer risk.

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+ Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article

Corresponding Author: Alex Trafford, MSc, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine, and Health, University of Manchester, Oxford Road, Stopford Bldg, Room 1.136, Manchester M13 9PT, United Kingdom (alex.trafford@ postgrad.manchester.ac.uk).

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soriasis is a common, chronic inflammatory skin disease with prevalence estimates varying globally in adults from 0.91% in the United States to 8.50% in Norway.¹ The condition also carries significant physical and psychosocial detriment.² The extent of the burden imposed by psoriasis is further exacerbated through numerous comorbidities that include depression, cardiovascular disease, and psoriatic arthritis.³ In contrast to the relatively wellestablished nature of the associations between these comorbidities and psoriasis, the association between cancer and psoriasis is much less clear, particularly for site-specific cancers. Despite this lack of clarity, the plausibility of the association is supported through the role of inflammation in the pathogenesis of psoriasis, with chronic inflammation previously linked to increased cancer risk.⁴ Treatments, including the use of immunomodulatory therapies, may also increase the risk of developing cancer. Furthermore, the prevalence of known cancer risk factors such as smoking, excessive alcohol consumption, and obesity has been reported to be increased in people with psoriasis.³

An earlier systematic review⁵ reported an increased risk of developing several cancers in people with psoriasis. Despite the usefulness of this review, it included some cancer risk estimates that only considered psoriatic arthritis, thus limiting the generalizability of results to those people with psoriasis only. A further limitation of this study was a search strategy that resulted in the omission of several studies on multiple autoimmune conditions, which also reported separate risk estimates for psoriasis. Given these limitations, the main aim of our study was to conduct a comprehensive critical review and meta-analysis of observational studies to ascertain the risk of cancer incidence in people with psoriasis. In addition to providing the first meta-analysis, to our knowledge, of cancer mortality risk in people with psoriasis, we also aimed to understand how the risk of cancer varied according to psoriasis severity and the level of adjustment for lifestyle factors.

Methods

Search Strategy and Eligibility Criteria

Six electronic databases (MEDLINE, Embase, MEDLINE in Process and other nonindexed citations, Cochrane Central Register, Web of Science, and LILACS [Literatura Latino-Americana e do Caribe em Ciências da Saúde]) were searched from inception to November 15, 2017, for relevant studies. The details of the search strategy for MEDLINE and Embase are presented in eTable 1 in the Supplement. Reference lists of included studies were also hand searched. All included studies had to meet the following eligibility criteria: cohort or casecontrol study design; at least 1 study group of patients with psoriasis; and a comparison group involving patients without psoriasis or the general population. Included studies were also required to investigate cancer occurrence or cancer mortality. Case-control studies that examined cancer risk for a range of autoimmune disorders were also eligible for inclusion if data were provided separately for those individuals with psoriasis. No restrictions were applied to language, geographic

Key Points

Question What is the risk of cancer incidence and cancer mortality in people with psoriasis?

Findings This systematic review and meta-analysis included 58 unique observational studies (50 reporting on cancer incidence and 15 on cancer mortality, including 7 reporting on both). The overall risk of developing cancer was significantly elevated in people with psoriasis and for a number of site-specific cancers; the risk of cancer mortality was found to be elevated in those with severe psoriasis.

Meaning These findings suggest that cancer is an important comorbidity in people with psoriasis, and dermatologists should be aware of this increased risk; further studies are needed to improve our knowledge about the underlying mechanisms of this increased risk.

region, or study period. The University of Manchester institutional review board determined that approval was not required for this study design. This study followed the Metaanalysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (eTable 2 in the Supplement).

Study Selection and Data Extraction

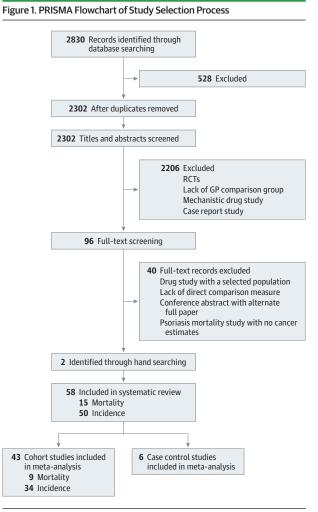
One author (A.M.T.) screened all titles and abstracts. Articles were sorted as definitely include, possibly include, and exclude. Articles classed as possibly include were reviewed by 4 authors (A.M.T., R.P., E.K., and D.M.A.) to determine whether the study was eligible for inclusion. Data extraction for all included studies was performed by 1 author (A.M.T.), with any issues requiring further clarification rectified through consultation with the other 3 reviewing authors. When more than 1 risk estimate was presented in a study report, the one with the greatest level of adjustment for potential confounding factors was extracted.⁶

Critical Appraisal Tool and Risk of Bias Assessment

To assess the risk of bias in the included cohort and casecontrol studies, the Newcastle-Ottawa Scale tool was used. Using the tool, each study was judged on 8 items in 3 categories, including the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure of interest for case-control studies or the outcome of interest for cohort studies. Studies that received 8 or 9 of a possible 9 points were regarded as high quality, whereas studies that received 6 or 7 were regarded as fair quality, and those that received 5 or less were regarded as low quality.⁷

Data Analysis

Data were analyzed from April 9, 2018, through February 22, 2019. To account for between-study heterogeneity,⁸ a metaanalysis was performed using a Der Simonian-Laird randomeffects model, with effect estimates from different studies combined through the generic inverse variance approach. For cohort studies, risk estimates were reported through risk ratios (RR), incidence rate ratios, incidence density ratios, hazard ratios, or standardized incidence/morbidity or mortality



GP indicates general population; RCT, randomized clinical trial.

ratios. These estimates were considered relative measures of risk and were therefore pooled. Included case-control studies reported risk estimates through odds ratios. Given the differences in study design, case-control studies were examined separately from cohort studies.

We also separately analyzed study estimates restricted to people with severe psoriasis and those including people with all severities of psoriasis. Studies were categorized as involving people with severe psoriasis if their study groups involved people who had received systemic treatment for psoriasis (including methotrexate sodium, cyclosporin, acitretin, etretinate, phototherapy, or biologicals) or had been hospitalized for psoriasis.

Studies were also grouped into 2 categories according to the level of adjustment for potential confounding. Level 1 studies adjusted for age and sex, whereas level 2 studies adjusted for age, sex, and at least 1 other confounding factor (such as smoking status, alcohol consumption, or body mass index). When more than 1 study provided an estimate using the same base population, the study reporting on the most complete data was included. Estimates calculated for separate subgroups, such as mild psoriasis and severe psoriasis, within the same study were combined before meta-analysis if the pooled estimate was more relevant to the metaanalysis (eMethods in the Supplement).

Heterogeneity in the pooled analyses was evaluated through the I^2 statistic⁸ and corresponding 95% CIs. The calculation of CIs was not possible for pooled estimates with less than 3 studies. All analyses were performed using Stata, version 15 (StataCorp LLC). Two-sided P < .05 indicated significance.

Results

Study Selection and Characteristics

Excluding duplicates, 2302 studies were identified through database searching. Through title and abstract screening, 2206 studies were excluded for reasons noted in Figure 1. Full-text screening excluded a further 40 studies. Hand searching identified 2 additional studies, leaving the total number of included studies at 58, with 50 of those investigating the risk of cancer⁹⁻⁵⁸ and 15 investigating cancer mortality^{13,15,32,33,41,48,54,59-66} (7 studies^{13,15,32,33,41,48,54} reported on both). Of the 50 cancer incidence studies, 28 considered only site-specific malignant neoplasms, with the remaining 22 considering all and site-specific malignant neoplasms. In contrast, of the 15 cancer mortality studies, only 1 study considered all and site-specific malignant neoplasms, with 6 studies considering only all malignant neoplasms and 8 considering only site-specific malignant neoplasms. The characteristics of the cancer incidence and cancer mortality studies are summarized in Table 1 and Table 2, respectively.

Study Quality

For the 50 studies examining cancer incidence, quality assessment ratings were mostly fair (29 [58%]) and the remainder graded as low (8 [16%]) and high (13 [26%]). The 15 studies of cancer mortality generally had much better quality, with most of these studies being high (8 [54%]); the remaining studies were graded as fair (5 [33%]) and low (7 [13%]). For cancer incidence and cancer mortality studies, quality was mostly lowered as a result of study participant selection. The comparability of study and comparison cohorts through matching or later adjustment also presented as an issue for a considerable number of studies. Low-quality outcome ascertainment and follow-up was the least common reason for low quality (10 studies [17%]).

Psoriasis and the Risk of Cancer Incidence All Cancers

A total of 22 cohort studies^{11,13,14,17-19,24,27-31,34,36,39,40,42,44,46,47,54,55} reported estimates of risk of all cancer incidence in people with psoriasis. Nine severe psoriasis studies^{11,18,30,34,40,42,46,47,55} were suitable for inclusion in the meta-analysis (**Figure 2**A), producing a significantly elevated pooled RR of 1.22 (95% CI, 1.08-1.39) with high heterogeneity (I^2 = 89.8% [95% CI, 82.8%-93.9%]). When taking into account psoriasis of all severities, 7 studies^{13,14,18,24,36,39,47} were included in the meta-analysis (Figure 2A), producing a significantly elevated pooled RR of 1.18 (95% CI, 1.06-1.31) with similarly high heterogeneity (I^2 = 90.2%

	Study Design (Outcome		Population (No. of Part	ticipants)	Duration	
Source	Measure)	Cancer Type	Study	Comparison	of Follow-up	Adjustment for Confounders
Alderson and Clarke, ¹¹ 1983	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis in Scottish discharge records (8405)	Scottish, English, and Welsh general population (NA)	Mean: 11.5 y	Standardized: age, sex, and CT
Anderson et al, ¹² 2009	Case-control (OR)	Lymphocytic malignant neoplasms	Patients with lymphocytic cancer in Medicare database (33 721)	Cancer-free patients in Medicare database (122 531)	NA	Matched: age, sex, and CT Adjusted: age, sex, CT, race, and use of health care services
offeta et al, ¹³ 001	Cohort (SIR)	All malignant neoplasms	Discharged patients with psoriasis from Swedish health database (9773)	Swedish general population (NA)	Mean: 11 y	Standardized: age, sex, and CT
Brauchli et al, ¹⁴ 2009	Cohort with nested case-control (IRR)	All malignant neoplasms	Patients with psoriasis in GPRD (33 760)	Psoriasis-free patients in GPRD (36 702)	Mean: 4.6 y	Matched: age, sex, CT, GP practice and years in GPRD Adjusted: age, sex, CT, smoking status, and BMI
Castro et al, ¹⁵ 2014	Cohort (SIR)	Hepatobiliary malignant neoplasms	Patients with psoriasis in the Swedish hospital discharge register (NR)	Swedish general population not hospitalized for any autoimmune disease (NA)	Mean: <1 y	Standardized: age, sex, CT, region and socioeconomic status Adjusted: smoking and alcoholism
Chen et al, ¹⁶ 2013	Cohort (RR)	Keratinocyte	Patients with psoriasis in 3 population-based cohort studies (3216)	Psoriasis-free patients in 3 population-based cohort studies (185 190)	NR	NR
Chen et al, ¹⁷ 2011	Cohort (HR)	All malignant neoplasms	Patients with psoriasis patients from NHIRD (3686)	Psoriasis-free patients from LHID (200 000)	Mean (psoriasis): 4.58 y Mean (control):	Adjusted: age, sex, and treatment modalities
chiesa et al, ¹⁸ 1015	Cohort (HR)	All malignant neoplasms	Any patients with psoriasis in THIN	Psoriasis-free patients in THIN	6.68 y Mean (psoriasis): 6.06-6.22 y	Matched: age and practice
			database (198 366)	database (937 716)	Mean (controls): 6.39-6.57 y	Adjusted: age, sex, BMI, smoking, and alcohol consumption
hiou et al, ¹⁹ 1016	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis in NHID of Taiwan (6835)	Psoriasis-free patients in NHID of Taiwan (21 226 181)	Median: 11 y	Standardized: age
Cooper et al, ²⁰ 1996	Case-control (OR)	Lymphocytic malignant neoplasms	Patients with leukemia identified through cancer treatment clinical	Random population sample attained through digit dialing (637)	NA	Matched: age, sex, race, region of residence Adjusted: age, sex, race, educational level, and smoking
0ai et al, ¹⁰ 1016	Cohort (RR)	Keratinocyte	trials (624) Women with psoriasis in the NHS I and II (2645)	Women without psoriasis in the NHS I and II (155 289)	Total: 2 487 941 person-years	Adjusted: age, BMI, exercise, alcohol intake, smoking, family history of melanoma, nevi counts, susceptibility to burn, hair color, number of severe sunburns, and U index at birth and ages 15 and 30
geberg et al, ²¹ 2016	Cohort (IRR)	Skin malignant neoplasms	Patients with skin cancer from Danish Healthcare database (56 907)	Skin cancer-free patients from Danish Healthcare database (5 484 010)	Maximum: 16 y	Adjusted: age, sex, socioeconomic status, ethnic origin, and phototherapy
ingels et al, ²²	Case-control	Lymphocytic	Patients with	Cancer-free	NA	Matched: age, sex, CT, and race
2016	(OR)	malignant neoplasms	lymphocytic cancer in the SEER-Medicare database (19078)	individuals in the SEER-Medicare database (200 000)		Adjusted: age, sex, CT of case/control selection, race, and number of provider claims
allah et al, ²³ 2014	Cohort (SIR)	NHL	Patients with psoriasis in Swedish health care databases (131 215)	Psoriasis-free patients in Swedish health care databases (NA)	Mean (psoriasis): 7.1 y	Standardized: age, sex, CT, region and socioeconomic status Adjusted: smoking and BMI
rentz and Ilsen, ²⁴ 999	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis discharged from hospital (6905)	Psoriasis-free individuals from the Central Population Register (NA)	Mean: 9.3 y	Standardized: age, sex, and CT
Gelfand et al, ²⁵ 2003	Cohort (HR)	Lymphocytic malignant neoplasms	>65 Patients with psoriasis in GPRD (2718)	Psoriasis-free patients in the GPRD (105 203)	Median (psoriasis): 38.75 y Median (psoriasis free): 46 y	Adjusted: age and sex
Gelfand et al, ²⁶ 2006	Cohort (HR)	Lymphocytic malignant	Patients with psoriasis in GPRD	Psoriasis-free patients in GPRD	Mean (control): 5.61 y	Matched: CT and practice
		neoplasms	(153 197)	(765 950)	Mean (all psoriasis): 4.54 y	Adjusted: age and sex

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	Study Design		Population (No. of Participants)			
Source	(Outcome Measure)	Cancer Type	Study	Comparison	Duration of Follow-up	Adjustment for Confounders
Gu and Nordstrom, ²⁷ 2017	Cohort (SIR)	All malignant neoplasms	Patients aged <18 y with psoriasis in IMS Health plan database (13 174)	General population from SEER database (NA)	Mean (psoriasis): 1.5 y Mean (psoriasis free): 1.6 y	Matched: age, sex, CT, region, and duration of enrollment Standardized: age and sex
Hannuksela et al, ²⁸ 1996	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis treated with trioxsalen PUVA in Finnish hospitals (527)	Finnish general population (NA)	Mean: 10.8 y	Standardized: age and sex
Hannuksela- Svahn et al, ²⁹ 1999	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis treated with trioxsalen PUVA in Finnish and Swedish hospitals (944)	Finnish and Swedish general population (NA)	Mean: 14.7 y	Standardized: sex
Hannuksela- Svahn et al, ³⁰ 2000	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis in the Finnish hospital discharge records (5687)	Finnish general population (NA)	Mean: 14 y	Standardized: age, sex, and CT
Hannuksela- Savhn et al, ³¹ 1999	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis treated with methoxypsoralen-8 PUVA in Finnish hospital discharge records (158)	Finnish general population (NA)	Mean: 7.6 y	Standardized: age, sex, and CT
Hemminki et al, ³² 2013	Cohort (SIR)	Brain malignant neoplasms	Patients with psoriasis in hospital discharge records (19 777)	Swedish general population (NA)	Mean: 11.9 y	Standardized: age, sex, CT, region and socioeconomic status Adjusted: obesity, smoking, alcohol, and socioeconomic
Hemminki et al, ³³ 2012	Cohort (SIR)	Female malignant neoplasms	Patients with psoriasis in hospital discharge records (8162)	Swedish general population (NA)	Total (psoriasis): 275 971 person-years	features Standardized: age, sex, CT, region and socioeconomic status Adjusted: obesity, smoking, alcohol, parity, and age at first birth
Ji et al, ³⁴ 2009	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis previously hospitalized in Sweden (15 858)	Swedish general population (NA)	Median: 10 y	Standardized: age, sex, period, socioeconomic status, residential area, age at first birth, and parity
Kim et al, ³⁵ 2015	Cohort (HR)	hort (HR) Cervical malignant	Female patients with psoriasis from 2 US	Female patients with hypertension from	Mean (psoriasis): 2.0 y	Adjusted: age, comorbidity score, No. of prescription drugs,
		neoplasms	health plans (34 665)	2 US health plans (533 332)	Mean (psoriasis free): 2.1 y	 alcoholism, smoking, substance abuse, sexually active status, STI presence, contraception use, HPV vaccine, diabetes, liver disease, systemic drugs, steroids, NSAIDs, and use of health care services
Lan et al, ³⁶ 2012	Nested case-control (HR)	All malignant neoplasms	Patients with psoriasis in the NHI (8180)	Psoriasis-free patients in the NHI (163 600)	NR	Matched: age and sex Adjusted: age, sex, hypertension,
Lanoy et al, ³⁷ 2010	Case-control (OR)	All malignant neoplasms	Elderly patients with cancer in the SEER-Medicare database (36 092)	Elderly cancer-free patients in the SEER-Medicare database (178 452)	NA	dyslipidemia, and diabetes Adjusted: age, sex, CT, and No. of physician claims
Lee et al, ³⁸ 2012	Cohort (IDR)	Skin malignant neoplasms	Patients with psoriasis in the LHID (7061)	Psoriasis-free patients in the LHID (1 000 000)	Mean: 4.8 y	Standardized: age and sex
Li et al, ³⁹ 2016	Cohort (HR)	All malignant neoplasms	Female patients with psoriasis in the NHS (2182)	Female psoriasis-free patients in the NHS (62 808)	Total: 22 132 person-years	Adjusted: age, BMI, alcohol consumption, physical activity, physical examination, multivitami use, smoking status, family history of cancer, contraceptive use, menopause status, history of benign breast disease, family history of breast cancer, age at first birth and parity, height, melanoma plus hair color, childhood tendency to sunburn or tan, No. of childhood sunburns, family history of melanoma, mole count, lifetime sun exposure, UV index, use of Als, hypertension,

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	Study Design (Outcome		Population (No. of Part	ticipants)	Duration	
Source	Measure)	Cancer Type	Study	Comparison	of Follow-up	Adjustment for Confounders
Lindelöf et al, ⁴⁰ 1990	Cohort (RR)	All malignant neoplasms	Patients with psoriasis in Swedish outpatient records (20 328)	Swedish general population (NA)	NR	Standardized: age and sex
iu et al, ⁴¹ 2013	Cohort (SIR)	Urological malignant neoplasms	Patients with psoriasis in Swedish outpatient records (19 777)	Swedish outpatients with no record of 33 selected AIs (NA)	Total (psoriasis): 275 971 person-years	Standardized: age, sex, CT, region and socioeconomic status Adjusted: obesity, smoking, and alcohol abuse
Margolis et al, ⁴² 2001	Cohort (RRR)	All malignant neoplasms	Patients with psoriasis from a US claims database (16 519)	Patients with hypertension from the same claims database (234 304)	Mean (severe psoriasis): 2.36 y Mean (less severe psoriasis): 2.27 y Mean (hypertension): 2.43 y	Adjusted: age, sex, and region
McKenna et al, ⁴³ 1996	Cohort (OER)	Keratinocyte	Patients with psoriasis from the Belfast city hospital (246)	General population from North Humberside (NA)	Median: 9.5 y	Standardized: age and sex
Olsen et al, ⁴⁴ 1992	Cohort (RR)	All malignant neoplasms	Patients with psoriasis in the Danish outpatient records (6910)	Danish general population (NA)	Mean: 5.1 y	Standardized: age, sex, and CT
Paradisi et al, ⁴⁵ 2017	Cohort (RR)	Keratinocyte	Patients with psoriasis in hospital records (72 739)	Patients undergoing vascular surgery in same hospital records (25 956)	NR	Adjusted: age, sex, and phototherapy
Paul et al, ⁴⁶ 2003	Cohort (SIR)	All malignant neoplasms	Patients with psoriasis (1252)	General population from the country of the case (NA)	Median: 4.5 y	Standardized: age, sex, and country
Prizment et al, ⁴⁷ 2011	Cohort (HR)	All malignant neoplasms	Female patients with psoriasis, aged >65 y, in the IWHS (719)	Female psoriasis-free patients in the IWHS (32 191)	Mean: 11.8 y	Standardized: age Adjusted: age, BMI, educational level, smoking, HT use, physical activity, and No. of live births
Reddy et al, ⁴⁸ 2017	Cohort (HR)	Melanoma and hematological cancer	Patients with psoriasis in the KPSC records (8161)	Psoriasis-free patients in the KPSC records (807 604)	NR	Matched: age and sex Adjusted: race, treatments, and
Shapiro et al, ⁴⁹ 2013	Case-control (OR)	Skin malignant neoplasms	Patients with psoriasis in inpatient records (1079)	Patients with dermatitis in inpatient records (1079)	NA	Charlson comorbidity index Matched: age and sex
Smedby et al, ⁵⁰ 2006	Case-control (OR)	Lymphocytic malignant neoplasms	Patients with lymphocyctic cancer in the SCALE study (3055)	General population (3187)	NA	Matched: age, sex, and country Adjusted: age, sex, country, smoking, BMI, educational level, blood transfusions, sun exposure, occupational exposure to pesticides, and family history of cancer
öderberg t al, ⁵¹ 2006	Case-control (OR)	Haematological malignant neoplasms	Patients with lymphocyctic cancer in the discharge registry (39 908)	General population (149 344)	NA	Matched: age, sex, and CT Adjusted: age, sex, and socioeconomic status
tern, ⁵² 006	Cohort (IRR)	Lymphoma	Patients with psoriasis in the PUVA follow-up study 1997-2005 (864)	General population using the SEER database (NA)	Total: 28 884 person-years	Standardized: age, sex, and CT Adjusted: age, skin type, methotrexate exposure, and UV-B exposure
tern et al, ⁵³ 002	Cohort (RR)	Skin malignant neoplasms	All patients with psoriasis and treated with PUVA after 1989 (892)	White men in the general population using the SEER database (NA)	NR	Standardized: age Stratified: treatment and period
tern and ange, ⁵⁴ .988	Cohort (SMR)	All malignant neoplasms	All patients with psoriasis treated with PUVA (1380)	General population from the SEER database (NA)	Total: 13 224 person-years	Standardized: age and sex Matched: age, sex, and region
tern et al, ⁹ 012	Cohort (IRR)	Skin malignant neoplasms	Patients with psoriasis treated with PUVA from all periods (1380)	White persons in the general population (NA)	Mean (cancer): 27 y Mean (cancer-free): 25 y	Adjusted: age, sex, PUVA, UV-B, skin type, and methotrexate exposure
Stern et al, ⁵⁵ 1997	Cohort (RR)	All malignant neoplasms	All patients with psoriasis treated with PUVA (1380)	White general population from SEER database (NA)	Median: 19.2 y	Standardized: age and sex

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	Study Design (Outcome		Population (No. of Par	ticipants)	Duration	
Source	Measure)	Cancer Type	Study	Comparison	of Follow-up	Adjustment for Confounders
Sunesen et al, ⁵⁶ 2010	Cohort (SIR)	Skin malignant neoplasms	Patients with psoriasis from the Danish national patient registry (24 308)	General population (NA)	Mean: 8.6 y	Standardized: age, sex, and CT
Tseng et al, ⁵⁷ 2013	Case-control (OR)	All malignant neoplasms	Patients with psoriasis in hospital records (447)	Psoriasis-free patients from the same hospital records (447)	NA	Matched: age, sex, and CT
Zhang et al, ⁵⁸	Case-control	Lymphocytic	Women with	General population	NA	Matched: age
2004	(OR)	malignant neoplasms	lymphocytic cancer in the CTR (601)	of Connecticut (717)		Adjusted: age, BMI, menopausal status, family history of NHL, race, educational level, tobacco use, and acohol consumption
			ndex; CT, calendar time;			MSC, nonmelanoma skin cancer;
			GPRD, General Practice		-	drug; OER, occurred to expected
			zard ratio; HT, hormonal			A therapy; RR, risk ratio; RRR, relative
1.2.	, ,	-	ntal Marketing Statistics;			logy Scale; SEER, Surveillance,
		Women's Health St	alth Insurance database;			dardized incidence ratio; exually transmitted infection;
IA, not applicable;	; NHI, national hea	Ith insurance; NHII search Database; N), NHI database;		provement Network	

[95% CI, 82.5%-94.6%]). In contrast, 1 hospital-based case-control study⁵⁷ also reported on the risk of all cancer in psoriasis of all severities, with a significantly reduced estimate; the corresponding odds ratio was 0.27 (95% CI, 0.16-0.44).

Site-Specific Cancers

For severe psoriasis studies, ^{10,11,15,18,21,28,30,33,34,39-43,46,47,52,54,55} meta-analysis was possible for a total of 22 site-specific cancers. Of these, incident risk was found to be significantly elevated in 8 site-specific cancers (Figure 3): squamous cell carcinoma (3 studies^{9,34,46}; RR, 11.74 [95% CI, 1.52-90.66]; I² = 99.7% [95% CI, 99.5%-99.8%]), lymphoma (4 studies^{18,42,46,52}; RR, 3.39 [95% CI, 1.34-8.62]; $I^2 = 85.6\%$ [95% CI, 64.6%-94.2%]), basal cell carcinoma (3 studies^{9,28,46}; RR, 3.17 [95% CI, 1.32-7.60]; I² = 57.3% [95% CI, 0%-87.8%]), keratinocyte (7 studies^{18,21,30,40,42,43,46}; RR, 2.44 [95% CI, 1.68-3.56]; *I*² = 90.9% [95% CI, 83.8%-94.9%]), esophagus (3 studies^{30,34,46}; RR, 2.34 [95% CI, 1.14-4.80]; *I*² = 56.4 [95% CI, 0%-87.5%]), liver (2 studies^{30,34}; RR, 1.94 [95% CI, 1.51-2.49]; I² = 0 [95% CI, not applicable [NA]), pancreas (3 studies^{18,30,34}; RR, 1.45 [95% CI, 1.15-1.83]; I² = 0 [95% CI, 0%-89.6%]), and bladder (3 studies^{11,28,41}; RR, 1.27 [95% CI, 1.06-1.52]; *I*² = 0 [95% CI, 0%-89.6%]). Meta-analysis was possible for 27 site-specific cancers from studies of all severities of psoriasis.^{10,13,14,16-18,23,24,26,35,38,39,44,45,47} Risk was significantly elevated in 12 site-specific cancers (Figure 3), including the oral cavity (2 studies^{13,24}; RR, 2.80 [95% CI, 1.99-3.93]; *I*² = 0 [95% CI, NA]), squamous cell carcinoma (4 studies^{10,13,16,24}; RR, 2.15 [95% CI, 1.32-3.50]; I² = 91.4% [95% CI, 81.2%-96.1%]), esophagus (3 studies^{13,14,44}; RR, 2.05 [95% CI, 1.04-4.07]; $I^2 = 49.1\%$ [95% CI, 0%-85.2%]), liver (2 studies^{13,44}; RR, 1.83 [95% CI, 1.28-2.61]; I² = 0 [95% CI, NA]), larynx (2 studies^{13,24}; RR, 1.79 [95% CI, 1.06-3.01]; $I^2 = 0$ [95% CI, NA]), keratinocyte (4 studies^{18,24,38,45}; RR, 1.71 [95% CI, 1.08-2.71]; I² = 98.3% [95% CI, 97.3%-99.0%]), kidney (3 studies^{13,24,39}; RR, 1.58 [95% CI, 1.11-2.24]; I² = 31.6% [95% CI,

0%-92.9%]), pancreas (4 studies^{13,14,18,44}; RR, 1.41 [95% CI, 1.16-1.73]; *I*² = 18.3% [95% CI, 0%-87.5%]), lymphoma (4 studies^{14,18,26,38}; RR, 1.40 [95% CI, 1.24-1.57]; I² = 23.3% [95% CI, 0%-88.3%]), colorectum (3 studies^{14,17,39}; RR, 1.34 [95% CI, 1.06-1.70]; $I^2 = 0$ [95% CI, 0%-89.6%]), non-Hodgkin lymphoma (5 studies^{13,23,24,26,39}; RR, 1.28 [95% CI, 1.15-1.43]; $I^2 = 4.4\%$ [95% CI, 0%-80.1%]), and colon (4 studies^{13,18,24,47}; RR, 1.18 [95% CI, 1.03-1.35]; *I*² = 34.6% [95% CI, 0%-77.1%]). Meta-analysis of a further 7 site-specific cancers was also possible for 7 case-control studies of all severities of psoriasis.^{12,22,37,49,50,57,58} Cancer risk was significantly elevated in T-cell lymphoma (3 studies^{22,50,58}; RR, 2.65 [95% CI, 1.30-5.41]; *I*² = 80.2% [95% CI, 37.7%-93.7%]), marginal zone lymphoma (3 studies^{22,50,58}; RR, 1.31 [95% CI, 1.06-1.62]; $I^2 = 0$ [95% CI, 0%-89.6%]), and B-cell lymphoma (3 studies^{12,50,58}; RR, 1.20 [95% CI, 1.03-1.39]; *I*² = 0 [95% CI, 0%-89.6%]).

Psoriasis and Risk of Cancer Mortality

All Cancers

A total of 7 cohort studies^{13,54,59,61,64-66} considered the risk of overall cancer mortality in people with psoriasis. Four studies of severe psoriasis^{59,64-66} produced a pooled RR of 1.22 (95% CI, 1.08-1.38) with considerable heterogeneity ($I^2 = 54.3\%$ [95% CI, 0%-84.9%]) (Figure 2B). Only 2 studies^{61,66} reported mortality risk estimates from all cancers in people with psoriasis of all severities. Pooling of these 2 studies found no difference in risk of cancer mortality; the corresponding pooled RR was 1.05 (95% CI, 0.96-1.16) with slight heterogeneity ($I^2 = 30.5\%$ [95% CI, NA]) (Figure 2B).

Site-Specific Cancers

Meta-analysis of cancer mortality was possible for 7 sitespecific cancers from studies involving people with severe psoriasis.^{15,32,33,60,63,64} Of these 7 individual cancers, mortality risk was found to be significantly elevated in the following 3 sites: esophagus (2 studies^{60,63}; RR, 2.53 [95% CI, 1.87-3.41];

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	Study Design (Outcome		Population (No. of Parti	icipants)	Duration	
Source	Measure)	Cancer Type	Study	Comparison	of Follow-up	Adjustment for Confounders
Abuabara et al, ⁵⁹ 2010	Cohort (HR)	All malignant neoplasms	Patients with psoriasis in primary care records (3603)	Psoriasis-free patients in primary care records	Mean (psoriasis): 3.43 y Mean	Adjusted: age and sex
				(14330)	(psoriasis-free): 3.40 y	
Boffeta et al, ¹³ 2001	Cohort (SIR)	All malignant neoplasms	Discharged patients with psoriasis from Swedish health database (9773)	Swedish general population (NA)	Mean: 11 y	Standardized: age, sex, and CT
Castro et al, ¹⁵ 2014	Cohort (SIR)	Hepatobiliary malignant	Patients with psoriasis in the Swedish	Swedish general population not	Mean: <1 y	Standardized: age, sex, CT, region and socioeconomic status
		neoplasms	hospital discharge register (NR)	hospitalized for any autoimmune disease (NA)		Adjusted: smoking and alcoholism
Hemminki et al, ³²	Cohort (SIR)	Brain malignant	Patients with psoriasis in hospital discharge	Swedish general population (NA)	Mean: 11.9 y	Standardized: age, sex, CT, region and socioeconomic status
2013		neoplasms	records (19777)			Adjusted: obesity, smoking, alcohouse, and socioeconomic features
Hemminki et al, ³³	Cohort (SIR)	Female malignant	Patients with psoriasis in hospital discharge	Swedish general population (NA)	Total (psoriasis): 275 971	Standardized: age, sex, CT, region and socioeconomic status
2012		neoplasms	records (8162)		person-years	Adjusted: obesity, smoking, alcohouse, parity, and age at first birth
Hemminki et al, ⁶⁰ 2012	Cohort (HR and SMR)	Digestive tract malignant	Patients with psoriasis in hospital discharge	Swedish general population (NA)	Total (psoriasis): 222 027	Standardized: age, sex, period, region, and socioeconomic status
2012		neoplasms	records (15 592)		person-years	Adjusted: obesity, smoking, and alcohol use
Lee et al, ⁶¹ 2017	Cohort (SMR)	All malignant neoplasms	Patients with psoriasis in the NHI database (80 167)	Taiwanese general population (NA)	Mean: 6.34 y	Standardized: age, sex, and CT
Lindqvist et al, ⁶²	Cohort (HR)	Multiple	Patients with multiple	General population	NR	Matched: age, sex, and county
2017		myeloma	myeloma from Swedish cancer registry (8367)	with no hematological cancer (33 577)		Adjusted: age, sex, and year of diagnosis
Liu et al, ⁴¹ 2013	Cohort (SIR)	Urological malignant	Patients with psoriasis in Swedish outpatient	Swedish outpatients with no record of 33	Total (psoriasis): 275 971	Standardized: age, sex, CT, region and socioeconomic status
		neoplasms	records (19777)	selected AIs (NA)	perons-years	Adjusted: obesity, smoking, and alcohol abuse
Poikolainen et al, ⁶³ 1999	Cohort (SMR)	All malignant neoplasms	Patients with psoriasis in hospital discharge records (5687)	Finnish general population (NA)	Mean: 14 y	Standardized: age, sex, and CT
Reddy et al, ⁴⁸	Cohort (HR)	Melanoma and	Patients with psoriasis	Psoriasis-free	NR	Matched: age and sex
2017		hematological cancer	in the KPSC records (8161)	patients in the KPSC records (807 604)		Adjusted: race, treatments, and Charlson comorbidity index
Shu et al, ⁶⁴ 2011	Cohort (HR)	All malignant neoplasms	Patients with psoriasis in hospital discharge records (1746)	Psoriasis-free patients in hospital discharge records (1 011 757)	Median (psoriasis): 1.83 y Median (psoriasis-free): 3.1 y	Adjusted: age, sex, CT, smoking, alcohol consumption, and obesity
Stern and	Cohort (SMR)	All malignant	All patients with	General population	Total: 13 224	Standardized: age and sex
Lange, ⁵⁴ 1988		neoplasms	PUVA-treated psoriasis (1380)	from the SEER database (NA)	person-years	Matched: age, sex, and region
Stern and Huibregtse, ⁶⁵	Cohort (SMR and HR)	All malignant neoplasms	Patients with psoriasis from PUVA follow-up	White US general population (NA)	Total (psoriasis): 30 817	Standardized: age, sex, and CT
2011	anu mit)	πουριασπισ	study (1376)	population (NA)	person-years	Stratified: treatment, psoriasis severity, educational level, BMI, alcohol consumption, and smoking
Svedbom et al, ⁶⁶ 2015	Cohort (HR)	All malignant neoplasms	Patients with psoriasis in the VEGA register or	Swedish general population	Mean (mild psoriasis): 4.6 y	Matched: age, sex, and region
			Skane Health Care Register (39 074)	(154775)	Mean (severe psoriasis): 3.4 y	Adjusted: age, sex, and comorbidities

Abbreviations: AI, anti-inflammatory; BMI, body mass index; CT, calendar time; HR, hazard ratio; KPSC, Kaiser Permanente Southern California; NA, not available; NHI, national health insurance; NR, not reported; PUVA, psoralen–UV-A; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

 $I^2 = 0$ [95% CI, NA]), liver (2 studies^{63,64}; RR, 1.43 [95% CI, 1.09-1.88]; $I^2 = 0$ [95% CI, NA]), and pancreas (2 studies^{63,64}; RR, 1.31 [95% CI, 1.02-1.69]; $I^2 = 0.6\%$ [95% CI, NA]).

Subgroup Analysis

Of the 9 studies included in the meta-analysis of all cancer risk for people with severe psoriasis, 7 studies^{11,30,34,40,42,46,55}

conducted age and sex (level 1) adjustment, with the remaining 2 studies^{18,47} controlling for age, sex, and other factors (level 2) adjustment. Meta-analysis of studies with level 1 adjustment produced a pooled RR of 1.25 (95% CI, 1.08-1.45; $I^2 = 91.9\%$ [95% CI, 85.9%-95.4%]) (eFigure in the Supplement). Conversely, meta-analysis of studies with level 2 adjustment produced attenuated results (RR, 1.09 [95% CI.

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Figure 2. Risk of All Cancer Incidence and Mortality in Individuals With Psoriasis Stratified by Severity of Psoriasis

	Α	Cancer	incidence
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ource	No. of Events in Participants With Psoriasis	No. of Participants	RR (95% CI)	Favors Reduced Cancer Risk	Favors Increased Cancer Risk	Weight %
All psoriasis						
Frentz and Olsen, ²⁴ 1999	795	6905	1.40 (1.21-1.51)		-8	14.55
Boffetta et al, ¹³ 2001	789	9773	1.37 (1.28-1.47)		-	16.05
Lan et al, ³⁶ 2012	369	8180	1.20 (1.06-1.36)			13.98
Brauchli et al, ¹⁴ 2009	927	33760	1.13 (1.02-1.24)		-	15.06
Prizment et al, ⁴⁷ 2011	107	719	1.10 (0.90-1.40)	-		9.98
Chiesa et al, ¹⁸ 2015	6289	198366	1.06 (1.02-1.09)		=	16.92
Li et al, ³⁹ 2016	209	2182	1.02 (0.89-1.17)	-	-	13.45
Subtotal (1 ² = 90.2% [95% CI, 82.5%	%-94.6%]; P <.001)	1.18 (1.06-1.31)		\diamond	100
evere psoriasis						
Paul et al, ⁴⁶ 2003	47	1252	2.10 (1.60-2.90)			8.01
Margolis et al, ⁴² 2001	76	1101	1.78 (1.32-2.40)			7.98
Ji et al, ³⁴ 2009	1408	NA	1.33 (1.26-1.40)		-	14.06
Hannuksela-Svahn et al, ³⁰ 2000	533	5687	1.30 (1.20-1.40)		-	13.68
Prizment et al, ⁴⁷ 2011	22	719	1.20 (0.80-1.80)	_		5.80
Stern et al, ⁵⁵ 1997	195	1380	1.08 (0.93-1.24)		-	12.14
Chiesa et al, ¹⁸ 2015	2186	12290	1.08 (0.96-1.22)		-	12.76
Lindelöf et al, ⁴⁰ 1990	520	20328	0.96 (0.88-1.05)	4	-	13.47
Alderson and Clark et at, 11 1983	403	8405	0.95 (0.82-1.10)	-1	-	12.10
Subtotal (1 ² = 89.8% [95% CI, 82.8%	%-93.9%]; P >.001)	1.22 (1.08-1.39)		\$	100
			(D.1	i i 1	ו 0.

B Cancer mortality

Durce	No. of Events in Participants With Psoriasis	No. of Participants	RR (95% CI)	Favors Reduced Cancer Risk	Favors Increased Cancer Risk	Weight, %
ll psoriasis						
Svedbom et al, ⁶⁶ 2015	624	39074	1.16 (0.96-1.40)			19.50
Lee et al, ⁶¹ 2017	1831	80167	1.03 (0.98-1.08)			80.50
Subtotal (1 ² = 30.5% [95% CI, NA]	P=.23)		1.05 (0.96-1.16)		♦	100
evere psoriasis						
Abuabara et al, ⁵⁹ 2010	67	3603	1.41 (1.07-1.86)		_ 	14.44
Svedbom et al, ⁶⁶ 2015	84	4719	1.32 (1.03-1.69)			16.79
Shu et al, ⁶⁴ 2011	754	1746	1.26 (1.18-1.35)		=	42.62
Stern and Huibregtse, 65 2011	146	1376	1.02 (0.86-1.20)	-	-	26.15
Subtotal (1 ² = 54.3% [95% CI, 0%-	84.9%]; P=.09)		1.22 (1.08-1.38)		\diamond	100
			0.		i i i	1

NA indicates not available; RR, relative risk. Square size indicates the weight of the study; blue diamonds, the pooled RR size.

0.97-1.22]; $I^2 = 0$ [95% CI, NA]). Marked attenuation of all cancer incidence risk for all severities of psoriasis was also observed when comparing level 1 adjustment studies (3 studies^{13,24,36}; RR, 1.33 [95% CI, 1.23-1.44]; $I^2 = 49.9\%$ [95% CI, 0%-85.5%]) with level 2 adjustment studies (4 studies^{14,18,39,47}; RR, 1.07 [95% CI, 1.03-1.10]; $I^2 = 0$ [95% CI, 0%-84.7%]). Stratification of studies by the level of adjustment for 6 site-specific cancers was also undertaken for studies involving people with all severities of psoriasis. For 5 of these cancers, the pooled estimates were lower in studies involving level 2 adjustment. The risk of all cancer mortality in severe psoriasis was higher in 4 studies with level 1 adjustment, ^{13,54,59,66} with a pooled RR of 1.29 (95% CI, 1.17-1.42; $I^2 = 0$ [95% CI, 0%-84.7%]) compared with RR of 1.15

(95% CI, 0.94-1.41; I^2 = 81.2% [95% CI, NA]) for 2 studies with level 2 adjustment^{64,65} (eFigure in the Supplement). Low study numbers prevented further stratification for site-specific cancer mortality.

RR (95% CI)

Discussion

We found significant associations between psoriasis and the incidence of and mortality due to cancer involving a range of site-specific cancers. Cohort studies of all severities of psoriasis suggested a 1.18-fold increased risk of developing cancer compared with psoriasis-free populations. Evidence from cohort studies of severe psoriasis indicated a 1.22-fold

Figure 3. Risk of Site-Specific Cancer Incidence by Severity of Psoriasis

ancer Site	No. of Studies	RR (95% CI)	Favors Reduced Favors Increas Cancer Risk Cancer Risk	ed / ² Value,
ll psoriasis				
Oral cavity	2	2.80 (1.99-3.93)		0
SCC	4	2.15 (1.32-3.50)		91.4
Esophagus	3	2.05 (1.04-4.07)		49.1
Liver	2	1.83 (1.28-2.61)		0
Larynx	2	1.79 (1.06-3.01)		0
Keratinocyte	4	1.71 (1.08-2.71)		98.3
FGO	2	1.61 (0.97-2.65)		25.1
Kidney	3	1.58 (1.11-2.24)		31.6
Thyroid	3	1.46 (0.80-2.65)		0
Bladder	4	1.41 (0.94-2.11)		65.1
Pancreas	4	1.41 (1.16-1.73)		18.3
Lymphoma	4	1.40 (1.24-1.57)	-	23.3
Colorectum	3	1.34 (1.06-1.70)		0
BCC	3	1.29 (0.73-2.26)		97.2
Lung	6	1.28 (0.98-1.68)		87.7
NHL	5	1.28 (1.15-1.43)	-	4.4
Ovary	3	1.25 (0.88-1.78)		0
Leukemia	3	1.23 (0.85-1.78)		67.2
Colon	4	1.18 (1.03-1.35)		34.6
Melanoma	6	1.17 (0.82-1.66)		68.1
Rectum	2	1.10 (0.78-1.57)		41.0
Stomach	3	1.10 (0.84-1.42)		41.0 0
Breast	6	1.04 (0.98-1.11)		1.9
Prostate	5	1.03 (0.91-1.17)	_	26.8
Cervix	3			41.6
	2	0.98 (0.63-1.54)		
Brain		0.95 (0.50-1.79)		47.6
Endometrium	2	0.81 (0.40-1.63)	-	57.5
evere psoriasis		11 74 (1 52 00 66)		. 00.7
scc	3	11.74 (1.52-90.66)		→ 99.7
Lymphoma	4	3.39 (1.34-8.62)		
BCC	3	3.17 (1.32-7.60)		- 57.3
Keratinocyte	7	2.44 (1.68-3.56)		90.9
Esophagus	3	2.34 (1.14-4.80)		56.4
Liver	2	1.94 (1.51-2.49)		0
NHL	2	1.64 (0.99-2.72)		74.3
Leukemia	4	1.53 (0.92-2.55)		60.2
Pancreas	3	1.45 (1.15-1.83)		0
Lung	6	1.32 (0.94-1.86)		93.2
Colon	6	1.28 (0.97-1.69)		51.9
CNS	4	1.27 (0.82-1.97)		62.8
Bladder	3	1.27 (1.06-1.52)		0
Cervix	2	1.25 (0.92-1.70)		0
Rectum	3	1.24 (0.97-1.60)		0
Kidney	3	1.21 (0.96-1.52)		7.5
Breast	8	1.14 (0.98-1.33)	-	44.8
Melanoma	6	1.08 (0.91-1.30)	-	0
Prostate	3	1.01 (0.87-1.18)		18.2
Stomach	3	0.97 (0.59-1.62)		83.6
	2	0.88 (0.66-1.16)	_	0
Ovary	2	0.85 (0.66-1.08)	_	0

Original Investigation Research

BCC indicates basal cell carcinoma; CNS, central nervous system; FGO, female genital organs; NHL, non-Hodgkin lymphoma; RR, relative risk; and SCC, squamous cell carcinoma.

increased risk of developing cancer when compared with populations without psoriasis, a result not significantly different from that of all psoriasis severities. With regard to cancer mortality, a 1.22-fold increased risk of dying due to cancer compared with psoriasis-free populations was observed in studies of severe psoriasis. In contrast, no significantly increased risk of cancer mortality was found in studies of all severities of psoriasis. Subgroup analysis by level of adjustment for confounders found marked attenuation of all cancer incidence and mortality risks in studies that additionally controlled for smoking, alcohol consumption, and obesity.

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With regard to site-specific cancers, we observed elevated incident cancer risks for lymphoma, keratinocyte, esophageal, liver, and pancreatic cancers in studies of severe psoriasis and in those involving people with all severities of psoriasis. Similarly, esophageal, liver, and pancreatic cancers also demonstrated an increased risk when considering cancer mortality in studies of severe psoriasis.

A number of hypothesized explanations exist for the increased risk of cancer in people with psoriasis. First, psoriasis is a chronic inflammatory disease, and the link between chronic inflammation and cancer has been well reported in other conditions, such as Crohn disease and Barrett esophagus.⁴ This explanation may hold particular sway when considering the suggested increased risk of pancreatic cancer incidence in people with psoriasis. Indeed, previous studies have noted an association between psoriasis and pancreatitis,⁶⁷ with acknowledged links between pancreatitis and pancreatic cancer. Beyond the underlying inflammatory mechanisms of psoriasis, the use of immunomodulatory agents and potentially carcinogenic therapies in psoriasis treatment has also been explored as a mechanism for increased cancer risk, particularly for cancers such as lymphoma. The use of immunomodulatory agents and increased cancer incidence has previously been suggested in other conditions, such as rheumatoid arthritis. However, a meta-analysis of the association between rheumatoid arthritis and cancer suggested a lower risk of all cancer (standardized incidence ratio, 1.05; 95% CI, 1.01-1.09) compared with that found in psoriasis.⁶⁸ Of particular relevance in this regard are biological therapies, which are being increasingly used for the management of severe psoriasis. Although preliminary studies have suggested little to no increased risk of cancer incidence in patients with psoriasis receiving these therapies, further study allowing greater follow-up and increased power is required to properly examine the potential cancer risk, particularly for sitespecific cancers.⁶⁹ In contrast to this, the association between phototherapy in psoriasis and cancer incidence has been extensively explored, with an increased risk of squamous cell carcinoma and basal cell carcinoma being well established.9 Furthermore, the increased prevalence of known cancer risk factors in people with psoriasis, such as smoking, excessive alcohol consumption, and obesity, has also been posited as a plausible explanation for an association with cancer. The potential role of these lifestyle factors is strengthened by the attenuation of risk in those studies^{14,18,39,47,54,64} that adjusted estimates for lifestyle factors and the increased risk of site-specific cancers, such as esophageal cancer and liver cancer, which have been reported to be independently associated with obesity, smoking, and higher alcohol consumption.⁷⁰

Despite these findings, cancer currently receives relatively little focus in guidelines for the management of psoriasis, compared with other comorbidities, such as cardiovascular disease. The National Institute for Health and Care Excellence guidelines for the assessment and management of psoriasis⁷¹ and the Canadian guidelines for psoriasis management⁷² do not give any consideration to cancer as a

comorbidity of psoriasis. In addition, guidelines produced by the Scottish Intercollegiate Guidelines Network and the American Academy of Dermatology⁷³ give consideration only to lymphoma. The evidence from this meta-analysis not only suggests that cancer should be given more consideration as an important comorbidity of psoriasis but also begins to present evidence that this risk could be alleviated to some extent through lifestyle behavior change. Although potential drivers of lifestyle behavior change, such as structured weight reduction and psychological counseling for alcohol use disorders, have been considered as a means to reduce the severity of psoriasis and alcohol-related mortality,74 their implementation may have the concurrent effect of attenuating some of the cancer risk. Although it has been noted that lifestyle behavior change is challenging for health care professionals to implement,⁷⁵ the importance of a more holistic approach to psoriasis care involving lifestyle behavior change is reinforced through the results of this meta-analysis.

Limitations

To our knowledge, this is the only meta-analysis of cancer risk that has stratified by psoriasis severity and examined the risk of cancer mortality in people with psoriasis. The stratification provided greater insight into the factors that may be implicit in the association between psoriasis and cancer, because certain treatments are more prevalent in those with severe disease. Further value is provided by this study in the consideration of site-specific cancers.

Potential limitations also need to be acknowledged in interpreting the findings, particularly the high levels of heterogeneity between some studies. Given the observed heterogeneity, we used a random-effects model to metaanalyze studies and conducted subgroup analyses to try to explain heterogeneity. Of interest, heterogeneity was largely reduced for overall cancer risk for severe and all severities of psoriasis through the grouping of studies that adjusted risk estimates for established cancer risk factors.

With regard to adjustment for potential confounders, a possible limitation to the wider consideration of the association between psoriasis and cancer is the lens through which smoking, alcohol consumption, and obesity are considered, as confounding factors or ones that lie on the causal pathway. Because it is possible that these factors, particularly obesity, lie on the causal pathway, it may not be appropriate to consider them simply by adjustment.

Two other limitations, similarly to this study and the wider examination of the association between psoriasis and cancer, are the classification of psoriasis severity and the reporting of duration of treatment exposure. Because a large number of contemporary studies, including a considerable number in this meta-analysis, use electronic health record databases, which do not include the psoriasis area and severity index (PASI), little information is available regarding the risk of cancer according to PASI-classified psoriasis severity. Indeed, only Dai et al (2016)¹⁰ presented the risk of cancer account for psoriasis severity or, as in this study, were required to use potentially suboptimal proxies

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to determine severe psoriasis, such as the receiving of systemic therapies or hospitalization for psoriasis. Although this study did not focus on cancer risk according to specific treatments for psoriasis, it was notable that very few included studies reported on the length of treatment exposures, and in those that did, duration of exposure was often only provided for phototherapy. Future studies providing detailed information regarding the length of exposure to treatments, using registries such as the British Association of Dermatologists Biologic and Immunomodulators Register, are essential to understand the role of psoriasis treatments in the association between the condition and cancer.

Conclusions

People with psoriasis have an elevated risk of developing or dying of cancer, particularly for a number of site-specific cancers. To improve the understanding of the link between psoriasis and cancer, further population-based studies are needed. Where possible, considering the association according to different severities of psoriasis would be beneficial. Understanding the role of lifestyle factors in any increased cancer risk remains challenging, but studies giving greater consideration of these factors would be of benefit.

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Author Affiliations: Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine, and Health, University of Manchester, Manchester, United Kingdom (Trafford, Parisi, Ashcroft); School of Health Sciences, National Institute for Health Research (NIHR) School of Primary Care Research, Division of Population Health, Faculty of Biology, Medicine, and Health. Health Services Research and Primary Care, University of Manchester, Manchester, United Kingdom (Kontopantelis); Dermatology Centre, NIHR Manchester Biomedical Research Centre, Faculty of Biology, Medicine, and Health, Salford Royal NHS Foundation Trust, University of Manchester, Manchester, United Kingdom (Griffiths).

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