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Personal history of psoriasis and risk of incident cancer among women: a population-based cohort study

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DEAR EDITOR

Psoriasis is a chronic inflammatory skin disorder. The pathophysiology is characterized by T-cell-mediated keratinocytic hyperproliferation and inflammatory changes[1]. Inflammation substantially contributes to the development and progression of cancers, with both local immune response and systemic inflammation play dramatic roles. The chronic, inflammatory state induced by psoriasis may therefore be associated with neoplastic diseases[2,3]. Most prior studies on psoriasis and cancer were based on moderate-to-severe

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psoriasis in clinical settings, and results for most cancers other than cutaneous squamous cell carcinoma (SCC) and Hodgkin lymphoma have been inconclusive (Discussion, Supplementary File).

We systematically examined the association between personal history of psoriasis and risk of incident cancer [other than keratinocyte carcinoma (KeraC, also known as non-melanoma skin cancer, i.e. SCC and basal cell carcinoma), based on a prospective analysis of the Nurses' Health Study (NHS, Supplementary file). In 2008, we queried NHS participants if they had physician-diagnosed psoriasis and the year of diagnosis (1997 or before, 1998-2001, 2002-2005, 2006-2007, or 2008)[4]. We confirmed self-reported psoriasis by using the Psoriasis Screening Tool (PST) questionnaire, which is 99% sensitive and 94% specific for psoriasis in a hospital-based pilot study[5]. We asked about the involved body surface area (BSA) when psoriasis was at its worst, measured using the palm (i.e. the subject's flat hand and thumb together, fingers not included). For cancer outcomes, only confirmed invasive cases after medical record review were included, except for breast cancer and bladder cancer, which included both invasive and *in situ* cases.

Among participants with information on history of psoriasis, we excluded psoriasis cases that responded to PST but were not verified or cancers occurring at or before 1997 (Supplementary Figure 1). Person-years of follow-up were calculated from the return of the 1996 questionnaire to the date of diagnosis of the first primary cancer, death, the last questionnaire response, or June of 2012, whichever came first. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of total cancer and major individual cancers, using Cox proportional hazards models, stratified by age and 2-year interval. Details on the covariates and other statistical analysis methods are shown in the Methods, Supplementary File.

Among a total of 64,990 participants, 2,182 (3.4%) psoriasis cases were diagnosed as of 2008. Of them, 1,292 (92.0%) had mild psoriasis (≤2 palms' involvement). Information on psoriasis and characteristics of the participants in 1996 are shown in the Results, Supplementary File.

During the follow-up (1996-2012), 8,348 cancer cases were identified (Table 1). We did not find an altered risk of total cancer associated with personal history of psoriasis (multivariate-adjusted HR=1.02; 95% CI: 0.89-1.17). In the analysis of individual cancers, personal history of psoriasis was associated with an increased risk of melanoma (HR=1.95, 95% CI: 1.21-3.13) and kidney cancer (HR=2.50, 95% CI: 1.27-4.92) (Table 1).

We conducted additional analyses by excluding self-reported psoriasis cases that were not reached for validation or did not respond to the validation questionnaires. The associations appeared even stronger (Table 2). Subgroup analysis by psoriasis severity found that the associations were stronger among psoriasis with 1 or more palm's involvement. There is a trend towards increased risk of melanoma (P_{trend}=0.003) and kidney cancer with the increasing psoriasis severity (P_{trend}=0.0004) (Table 2).

In the analyses excluding all moderate-to-severe psoriasis (>2 palm areas' involvement), the associations for melanoma and kidney cancer remained significant. The associations for

melanoma and kidney cancer remained significant; the HR (95% CI) was 1.98 (1.22-3.23) for melanoma and 2.44 (1.19-5.00) for kidney cancer. We conducted a set of other sensitivity analyses and secondary analyses and did not find material change of the HRs (Methods and Results, Supplementary File).

Few studies have examined the association between psoriasis and risk of incident cancer based on a population-based cohort study. Several cohort studies based on registry datasets examined the association[6-12]. Four focused on one cancer type only[6,10-12] and a fifth evaluated total cancer but did not examine individual cancers[7]. The sixth and seventh studies comprehensively examined risk of individual cancers, but both only adjusted for few confounders[8,9]. Of them, three studies examined the association for melanoma but reported opposite associations[8-10]. None examined kidney cancer specifically. Comparisons of our findings with these studies are shown in the Results, Supplementary File.

The inflammation and oxidative stress might be the mechanisms underlying the associations with melanoma and kidney cancer, both of which have been linked with the elevated state of inflammation and oxidative stress (Supplementary File)[13-15].

For kidney cancer, subgroup analysis among those with normal BMI, non-hypertension, or non-smokers did not appreciably change the effect estimates (Supplementary File). Therefore, the association with psoriasis may not be confounded or mediated by these factors. In another analysis in this cohort, our group did not find a significant association between psoriasis and KeraC (manuscript under review elsewhere). The observed association for melanoma may not be greatly confounded or mediated by tendency to sunburns (surrogate for intermittent sun exposure), chronic sun exposure, and other risk factors that are more prevalent in psoriatics (Supplementary Table 1), which we have comprehensively adjusted for. This is also supported by the non-heterogeneous results we found for melanoma in sun-exposed sites or other sites (Supplementary File), as chronic sun exposure may be important, such as for lengtigo maligna melanoma.

Our study has some limitations. First, history of psoriasis was measured retrospectively and only at one time point based on self-report, misclassification was therefore possible. Second, we do not have information on psoriasis systemic therapies that typically apply to moderate-to-severe psoriasis and have been proposed to be trigger for cancers in psoriatics. In our study, the majority was mild psoriasis, and the findings persisted after excluding moderate-to-severe psoriasis measured by BSA. We do not have information on psoriasis phototherapy as well, which we are in the process of collecting the data. Third, we do not have the complete information on psoriasis severity measures other than BSA; evaluation on psoriasis severity is therefore restricted. Other limitations such as generalizability of the findings are discussed in the Supplementary File.

The results from a large, long-term followed cohort study suggest a positive association between personal history of psoriasis and risk of melanoma and kidney cancer. The association remained significant when we excluded moderate-to-severe psoriasis cases (>2 palm area). Further work is warranted to examine the association for psoriasis with and

without concomitant psoriatic arthritis and to collect information on use of systemic therapies and other measures of psoriasis severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Personal history of psoriasis and risk of first primary cancer (other than skin keratinocyte carcinoma) (1996-2012) [a]

	No psoriasis (935,227 person-years)	Psoriasis (22,132 person-years)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[b]
Total cancer	8139	209	1.06 (0.92-1.21)	1.02 (0.89-1.17)
Breast cancer[c]	4034	86	0.91 (0.73-1.12)	0.89 (0.71-1.10)
Colorectal cancer	697	20	1.19 (0.76-1.86)	1.11 (0.71-1.73)
Non-Hodgkin lymphoma	527	13	1.01 (0.58-1.75)	1.03 (0.59-1.78)
Endometrial cancer	515	7	0.60 (0.28-1.26)	0.54 (0.26-1.15)
Lung cancer	429	14	1.23 (0.72-2.09)	1.05 (0.61-1.79)
Melanoma[d]	380	18	2.00 (1.25-3.21)	1.95 (1.21-3.13)
Bladder cancer	232	7	1.20 (0.57-2.55)	1.10 (0.52-2.35)
Ovarian Cancer	194	6	1.25 (0.55-2.81)	1.28 (0.56-2.88)
Thyroid cancer	153	5	1.37 (0.56-3.33)	1.36 (0.56-3.32)
Kidney cancer[e]	137	9	2.74 (1.40-5.39)	2.50 (1.27-4.92)
Other Cancers[f]	841	24	1.03 (0.69-1.54)	0.97 (0.65-1.46)

CI, confidence interval; HR, Hazard Ratio

[a] Self-reported psoriasis cases that refused the diagnosis were excluded.

[b] Adjusted for age, BMI (<21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, 35.0-39.9, or ≥40.0 kg/m^2), alcohol consumption (none, 0.1-4.9, 5.0-9.9, or ≥10 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 metabolic equivalent hours/wk), physical examination (yes or no), multi-vitamin use (yes or no), smoking status (never, past, current smokers with 1-14, 15-24, or ≥25 cigarettes/d), and family history of cancer (yes or no) (except for the analysis of melanoma and breast cancer).

[c] Additionally adjusted for oral contraceptive use (never, past, or current), menopausal status and PMH use (pre-menopause, post-menopause without PMH use, post-menopause with PMH use), personal history of benign breast disease (yes or no), family history of breast cancer (yes or no), age at first birth and parity (nulliparous, age at first birth<25 and parity 1-2, age 25-29 and parity 1-2, age ≥30 and parity 1-2, age <25 and parity ≥3, or age 25-29 and parity ≥3, or age ≥30 and parity ≥3), age at menarche (≤12, 13, or ≥14), height (< 1.60, 1.60-1.64, 1.65-1.70, or ≥1.70 m) and BMI at age 18 (<20, 20-22.4, 22.5-24.9, 25-29.9, or ≥30 kg/m^2).

[d] Additionally adjusted for natural hair color (black, dark brown, light brown, blonde, or red), childhood tendency to sunburn (practically none, some redness only, burn, painful burn or burn with blisters), childhood tendency to tanning (practically none, little tan, average tan, or deep tan), number of teenage sunburns (none, 1-2, 3-5, 6-9, or ≥10), family history of melanoma (yes or no), mole count (none, 1-2, 3-4, 5-9, or ≥10), sun exposures at high school, age 25 to 35, 35 to 59, and 60 or older (≤1, 2-5, 6-10, or ≥11 hours/wk for each), and UV index at birth, age 15, and age 30 years (≤5, 6, or ≥7 for each).

[e] Additionally adjusted for history of use of NSAIDs (never, 1-3, 4-6, or >6 years), history of hypertension (yes or no), diabetes (yes or no), and parity (nulliparous, 1-2, or ≥3).

[f] Other individual cancers each with cases less than 100.

Table 2

Personal history of PST confirmed psoriasis and psoriasis severity and risk of melanoma and kidney cancer as the first primary cancer (1996-2012) [a]

	Person-years	Number of cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI) [b]
Analysis of melanoma [c]				
Ref: No psoriasis	930,950	378	1.00	1.00
Psoriasis	15,278	14	2.30 (1.35-3.92)	2.21 (1.29-3.77)
Categorized by psoriasis severity				
<1 palm area	9,730	8	1.94 (0.92-4.11)	1.84 (0.87-3.90)
≥1 palm area	5,548	6	2.69 (1.20-6.03)	2.65 (1.18-5.97)
P for trend by palm area (continuous)			0.002	0.003
Analysis of kidney cancer [d]				
Ref: No psoriasis	930,950	136	1.00	1.00
Psoriasis	15,278	7	3.15 (1.47-6.73)	2.88 (1.34-6.17)
Categorized by psoriasis severity				
<1 palm area	9,730	2	1.39 (0.34-5.61)	1.27 (0.31-5.12)
≥1 palm area	5,548	5	6.37 (2.60-15.57)	5.86 (2.39-14.39)
P for trend by palm area (continuous)			0.0002	0.0004

CI, confidence interval; HR, Hazard Ratio

[a] Self-reported psoriasis cases that refused the diagnosis or that did not get into the validation study were excluded.

[b] Adjusted for age, BMI (<21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, 30.0-32.9, 33.0-34.9, 35.0-39.9, or ≥40.0 kg/m^2), alcohol consumption (none, 0.1-4.9, 5.0-9.9, or ≥10 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 metabolic equivalent hours/wk), physical examination (yes or no), multi-vitamin use (yes or no), smoking status (never, past, current smokers with 1-14, 15-24, or ≥25 cigarettes/d),.

[c] Additionally adjusted for natural hair color (black, dark brown, light brown, blonde, or red), childhood tendency to sunburn (practically none, some redness only, burn, painful burn or burn with blisters), childhood tendency to tanning (practically none, little tan, average tan, or deep tan), number of teenage sunburns (none, 1-2, 3-5, 6-9, or ≥10), family history of melanoma (yes or no), mole count (none, 1-2, 3-4, 5-9, or ≥10), sun exposures at high school, age 25 to 35, 35 to 59, and 60 or older (≤1, 2-5, 6-10, or ≥11 hours/wk for each), and UV index at birth, age 15, and age 30 years (≤5, 6, or ≥7 for each).

[d] Additionally adjusted for history of use of NSAIDs (never, 1-3, 4-6, or >6 years), history of hypertension (yes or no), diabetes (yes or no), and parity (nulliparous, 1-2, or ≥3).