

CLINICAL REPORT

Hormonal Factors and Risk of Psoriasis in Women: A Cohort Study

Shaowei WU^{1,2}, Eunyoung CHO^{1,3,4}, Wen-Qing LI^{1,4}, Francine GRODSTEIN^{3,5} and Abrar A. QURESHI^{1,3,4}

¹Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, ²Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, ³Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, ⁴Department of Epidemiology, School of Public Health, Brown University, Providence, and ⁵Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

Previous studies suggest that hormonal factors modulate the natural course of psoriasis in women. However, the association of hormonal factors with psoriasis risk has not been assessed using prospective data. We carried out a thorough prospective analysis on the topic in 163,763 women in the Nurses' Health Study I and II. Participants provided information on age at menarche, parity, menopause status, and exogenous hormone use (oral contraceptive and postmenopausal hormone therapy) over the follow-up. We ascertained 1,253 incident psoriasis cases over 2 million person-years. Psoriasis risk appeared to be higher in women with always irregular menstrual cycles in adulthood (multivariate-adjusted hazard ratio=1.32, 95% confidence interval (CI): 1.01–1.73, compared with regular cycles) and surgical menopause (hazard ratio=1.19, 95% CI: 1.01–1.40, compared with natural menopause). Hormone therapy had suggestive but insignificant associations with psoriasis risk. Our results suggest little evidence for hormonal factors and risk of psoriasis in women that need further investigation. Key words: epidemiology; hormone; psoriasis; women.

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Abrar A. Qureshi, MD, MPH, Department of Dermatology, Warren Alpert Medical School, Brown University, 339 Eddy St, Providence, RI 02903, USA. E-mail: abrar_qureshi@brown.edu

Psoriasis is an immune-mediated chronic systemic disease that affects about 1.5–3% of the western population and over 125 million patients worldwide (1–3). Psoriasis has been associated with significant morbidity (4–6), as well as substantial economic costs in the general population (7, 8). Despite the high prevalence, the pathogenesis of this disease has not been fully elucidated. Knowledge on modifiable risk factors of psoriasis is critical for the prevention of the disease and subsequent adverse health outcomes. However, prospective data assessing the association between modifiable factors and the incidence of psoriasis have been limited. Specifically, it has been demonstrated that sex steroid hormones manifest a variety of biological and immunological effects in the skin (9, 10). For example, previous studies have demonstrated

that estrogen is associated with increases in skin thickness and skin collagen/dermal water contents, improved barrier function, and enhanced wound healing (10). Females are known to have a higher prevalence of a number of autoimmune diseases than men, suggesting that gonadal hormones may have a role in this sex difference (11). Pregnancy and menopause modulate the natural course of psoriasis in women, suggesting a female hormone-induced regulation of skin inflammation (12–14). For example, psoriasis has been shown to improve during pregnancy when compared to that before pregnancy, and the improvement is correlated with high estrogen levels but not progesterone levels (12). However, whether there is any association between postmenopausal hormone therapy (HT) and psoriasis risk in women has been unknown. No perspective population-based studies have investigated the potential association between hormonal factors and psoriasis risk among women. To address the hypothesis that hormonal factors may be associated with risk of psoriasis, we investigated hormone-related factors in association with incident psoriasis, based on data from two well-established cohorts of women, the Nurses' Health Study I (NHS I) and NHS II.

MATERIALS AND METHODS

The NHS I was established in 1976 when 121,701 married, registered, female nurses aged 30–55 years residing in the United States at the time of enrollment responded to a baseline questionnaire that included questions about their medical history and lifestyle risk factors. The NHS II was established in 1989 when 116,430 registered female nurses aged 25–42 years were enrolled using a mailed baseline questionnaire which inquired about medical history and lifestyle practices. Information on risk factors and health data was updated by biennially mailed questionnaires in both cohorts. The institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health approved the study. A detailed description on the assessment of endogenous and exogenous hormonal factors and covariates considered in the present study, case ascertainment for psoriasis, and statistical analysis could be found in Appendix S1. Briefly, we included women who returned the main questionnaires with psoriasis questions (see SFig. 1 in Appendix S1¹ for the derivation of the study participants). We used Cox proportional hazards analyses to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence

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intervals (CIs) of incident psoriasis associated with hormonal factors. Multivariate HRs were computed with adjustment for potential confounders which were selected based on previous literature from epidemiologic studies on psoriasis and associated risk factors and comorbidities (6, 15–19). Analyses were conducted within each cohort separately and the results were pooled using a random-effect model. All statistical analyses were conducted using Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc., Cary, NC). All statistical tests were 2-tailed, and the significance level was set at $p < 0.05$.

RESULTS

Among 74,533 women in the NHS I and 89,230 women in the NHS II (total $n = 163,763$), we confirmed a total of 1,253 incident psoriasis cases (613 in NHS I and 640 in NHS II) over 2,109,858 person-years of follow-up. The baseline characteristics of incident psoriasis cases with or without confirmation were similar: mean age, 48.5 vs. 48.9 years; BMI, 26.8 vs. 26.8 kg/m²; alcohol intake, 4.5 vs. 5.2 grams/day; physical activity, 18.5 vs. 17.8 metabolic-equivalent hours/week; current smoking, 18.4% vs. 18.0%; ever pregnant, 88.4% vs. 86.7%; ever HT use, 80.3% vs. 80.0% ($p > 0.10$ for all comparisons). Women not confirmed by the Psoriasis Screening Tool (PST) were excluded from the analyses. Table SI¹ shows characteristics of all study participants at baseline. Compared to never HT users, HT users were more likely to be past smokers and less likely to be current smokers, had a lower prevalence of natural menopause and a higher prevalence of surgical menopause, and were more likely to use oral contraceptive.

Menstrual factors. Age at menarche was not associated with psoriasis risk (Table I). Compared with women with regular cycles in adulthood, women with always irregular cycles had a moderately higher psoriasis risk (multivariate HR = 1.32, 95% CI: 1.01–1.73). Menopausal status was not associated with psoriasis risk. However, postmenopausal women with surgical menopause had a slightly higher psoriasis risk compared to women with natural menopause (HR = 1.19, 95% CI: 1.01–1.40). Postmenopausal women with prolonged length of ovulatory life had an insignificantly increased psoriasis risk (HR = 1.22, 95% CI: 0.98–1.52, ≥ 40 years vs. 35–39 years).

Reproductive factors. There was no evidence of an association between psoriasis risk and parous, age at first or last birth (Table II). Compared with women with only one child, women with multiple children (≥ 2) appeared to have a suggestive but insignificant lower psoriasis risk (HR = 0.85, 95% CI: 0.71–1.01,

P for trend = 0.41). Breast feeding duration was not associated with psoriasis risk in the pooled analysis. However, breast feeding duration was associated with a potentially lower risk in the NHS II, a cohort of younger women (HR = 0.69, 95% CI: 0.51–0.93, for breast feeding 24 months or longer vs. never).

Hormone use. Compared to never HT users, current users had a small, borderline increased psoriasis risk (HR = 1.22, 95% CI: 0.99–1.50), whereas past users had no increased risk (HR = 0.97, 95% CI: 0.79–1.19) (Table III). Analyses by HT type suggested that both use of unopposed estrogen or estrogen plus progestin showed insignificant positive associations with psoriasis risk. There was no association between oral contraceptive use and psoriasis risk.

Table I. Pooled hazard ratios of psoriasis according to menstrual factors in the Nurses' Health Study I (1996–2008) and II (1991–2005)^a

	Cases, Person- <i>n</i>	Person- years, <i>n</i>	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)	<i>p</i> ^c
Age at menarche					
≤11 years	323	493,404	1.11 (0.95–1.29)	1.03 (0.88–1.20)	0.61
12 years	355	603,372	1.00	1.00	
13 years	369	612,857	0.99 (0.83–1.19)	1.03 (0.89–1.19)	0.32
≥14 years	201	389,808	0.86 (0.71–1.04)	0.92 (0.77–1.09)	0.46
Menstrual cycle regularity at ages 18–22 years					
Regular	865	1,472,138	1.00	1.00	
Usually irregular	167	258,800	1.07 (0.66–1.71)	1.07 (0.65–1.78)	0.004
Always irregular	117	185,795	1.07 (0.89–1.30)	1.03 (0.85–1.25)	0.85
Menstrual cycle regularity in adulthood					
Regular	874	1,519,426	1.00	1.00	
Usually irregular	89	142,742	1.02 (0.82–1.27)	0.97 (0.78–1.21)	0.70
Always irregular	59	65,866	1.52 (1.17–1.98)	1.32 (1.01–1.73)	0.98
Menopause status					
Premenopause	448	987,868	1.00	1.00	
Postmenopause	744	1,006,779	1.31 (0.71–2.42)	0.77 (0.50–1.18)	0.37
Type of menopause ^b					
Natural menopause	405	571,027	1.00	1.00	
Surgical menopause	333	1,196,330	1.19 (1.02–1.38)	1.19 (1.01–1.40)	0.83
Age at menopause ^b					
<45 years	126	169,279	1.16 (0.93–1.44)	1.03 (0.82–1.30)	0.70
45–49 years	206	268,101	1.07 (0.90–1.28)	1.06 (0.89–1.27)	0.82
50–54 years	389	538,581	1.00	1.00	
≥55 years	60	71,487	1.41 (0.70–2.84)	1.59 (0.72–3.48)	0.10
Age at natural menopause ^b					
<45 years	32	45,821	1.13 (0.77–1.68)	1.04 (0.70–1.55)	0.96
45–49 years	121	170,777	1.06 (0.84–1.33)	1.01 (0.81–1.27)	0.54
50–54 years	202	294,776	1.00	1.00	
≥55 years	48	54,786	1.32 (0.90–1.95)	1.40 (0.86–2.28)	0.27
Length of ovulatory life ^b					
<30 years	82	106,571	1.25 (0.96–1.61)	1.28 (0.81–2.03)	0.44
30–34 years	137	175,267	1.20 (0.98–1.46)	1.19 (0.90–1.55)	0.95
35–39 years	343	494,985	1.00	1.00	
≥40 years	214	263,755	1.17 (0.98–1.39)	1.22 (0.98–1.52)	0.85

^aHazard ratios (HR) were further adjusted for body mass index (continuous), alcohol intake (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, or 30.0+ g/day), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, or 27.0+ METs-hours/week), smoking status (never, past, or current with 1–14, 15–24, or 25+ cigarettes/day), age at menarche (≤11, 12, 13, or ≥14), age at menopause (<45, 45–49, 50–54, or ≥55), type of menopause (natural or surgical), parity (nulliparous, 1, 2, 3, or ≥4), postmenopausal hormone use (never, past, or current use), and oral contraceptive use (never or ever). Results in two cohorts were pooled using the random-effect model. ^bAnalyses among postmenopausal women only. ^c p for heterogeneity between two cohorts using the Q statistic. CI: confidence interval.

Table II. Pooled hazard ratios of psoriasis according to reproductive factors in the Nurses' Health Study I (1996–2008) and II (1991–2005)^a

	Cases, n	Person-years, n	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)	p ^b
Nulliparous					
No	1,050	1,771,373	1.00	1.00	
Yes	193	285,753	1.19 (0.92–1.53)	1.13 (0.96–1.33)	0.42
Age at first birth					
<22 years	124	176,670	1.34 (0.78–2.29)	1.24 (0.66–2.35)	0.002
22–24 years	374	637,477	1.00	1.00	
25–29 years	398	720,366	1.00 (0.87–1.16)	1.04 (0.90–1.20)	0.82
≥30 years	154	289,592	0.97 (0.66–1.43)	1.02 (0.69–1.51)	0.07
Age at last birth					
<25 years	83	132,062	1.11 (0.87–1.42)	1.02 (0.79–1.32)	0.29
25–29 years	350	655,258	1.00	1.00	
30–34 years	390	665,671	1.04 (0.89–1.20)	1.08 (0.93–1.25)	0.75
≥35 years	197	341,726	1.00 (0.83–1.19)	1.07 (0.89–1.28)	0.91
Parity					
1	159	238,180	1.00	1.00	
≥ 2	891	1,533,194	0.81 (0.68–0.96)	0.85 (0.71–1.01)	0.88
2	382	705,163	0.80 (0.67–0.96)	0.83 (0.69–1.00)	0.33
3	272	473,997	0.78 (0.63–0.96)	0.82 (0.67–1.01)	0.87
≥4	237	354,034	0.82 (0.61–1.11)	0.87 (0.68–1.11)	0.49
p for trend			0.35	0.41	0.03
Breast feeding duration					
Never	316	447,568	1.00	1.00	
1–6 months	259	411,664	0.88 (0.71–1.10)	0.85 (0.67–1.07)	0.37
7–11 months	121	244,079	0.76 (0.61–0.94)	0.80 (0.65–1.00)	0.71
12–23 months	186	318,437	0.92 (0.67–1.27)	1.02 (0.79–1.31)	0.18
≥24 months	106	252,964	0.71 (0.44–1.15)	0.83 (0.56–1.23)	0.09
p for trend			0.39	0.88	0.03

Although the NHS I started 13 years before NHS II, the diagnostic date of psoriasis was ascertained in the NHS I from 1996. We do not have information on the diagnosis of psoriasis in the NHS I before 1996, and thus could not use the cohort data before 1996 in this particular analysis. ^aHazard ratios (HR) were further adjusted for the covariates listed in Table I footnote. Results in two cohorts were pooled using the random-effect model. ^bp for heterogeneity between two cohorts using the Q statistic. CI: confidence interval.

Table III. Pooled hazard ratios of psoriasis according to exogenous hormone use status in the Nurses' Health Study I (1996–2008) and II (1991–2005)^a

	Cases, n	Person-years, n	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)	p ^c
HT use status ^b					
Never	163	225,112	1.00	1.00	
Ever	541	716,677	1.05 (0.88–1.25)	1.09 (0.91–1.30)	0.62
Past	276	332,799	0.96 (0.79–1.17)	0.97 (0.79–1.19)	0.63
Current	265	383,878	1.15 (0.94–1.41)	1.22 (0.99–1.50)	0.74
<5 years	66	111,907	1.07 (0.77–1.48)	1.14 (0.82–1.58)	0.61
5–9 years	66	102,242	1.12 (0.83–1.51)	1.19 (0.88–1.61)	0.57
≥10 years	133	168,417	1.19 (0.94–1.51)	1.27 (0.99–1.62)	0.93
p for trend			0.07	0.21	0.71
Most recent HT type ^b					
Never	163	225,112	1.00	1.00	
E	255	327,867	1.11 (0.91–1.35)	1.13 (0.92–1.38)	0.62
E+P	189	260,490	1.03 (0.84–1.28)	1.08 (0.87–1.34)	0.44
Others	62	83,507	0.94 (0.70–1.26)	1.00 (0.74–1.34)	0.99
OC use status					
Never	354	578,616	1.00	1.00	
Ever	868	1,473,181	1.09 (0.93–1.28)	1.03 (0.86–1.24)	0.22

^aHazard ratios (HR) were further adjusted for the covariates listed in Table I footnote. Results in two cohorts were pooled using the random-effect model. ^bAnalyses among postmenopausal women only. ^cp for heterogeneity between two cohorts using the Q statistic. CI: confidence interval; E + P: estrogen + progestin combination; E: unopposed estrogen; OC: oral contraceptive; HT: postmenopausal hormone.

After the Bonferroni correction for multiple comparisons ($n = 16$), there was no significant association between examined hormonal factors and risk of psoriasis.

DISCUSSION

Our study provided the first comprehensive investigation of the association between hormonal factors and risk of incident psoriasis in women. After adjusting for other psoriasis risk factors and potential confounders, we found that always irregular menstrual cycle in adulthood and surgical menopause may be associated with a modestly increased risk of psoriasis among women. Other associations were only suggestive and largely insignificant (e.g., associations for HT use, parity and breast feeding duration).

Psoriasis is a disease characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes (1–3). Innate immune cells, including dendritic cells and macrophages, are activated in the inflammatory cascade and secrete inflammatory chemical signals (cytokines) such as tumor necrosis factor- α (TNF- α), interferon- α , interleukin-6, interleukin 12, and interleukin 23, leading to the differentiation of type 17 (Th-17) and type 1 (Th-1) helper T cells. T cells secrete mediators such as interleukin-17A and interleukin 7F that activate keratinocytes and induce the production of antimicrobial peptides, proinflammatory cytokines and chemokines. These soluble mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate in psoriasis (3). The role of estrogen in the inflammation, however, is complex. Estrogen has been shown to inhibit bone resorption and suppress inflammation in several animal models of chronic inflammatory diseases (e.g., arthritis), (20–22) but also induce proinflammatory effects in some chronic autoimmune diseases (e.g., systemic lupus erythematosus) in humans (23–25). The factors responsible for the confusion are diverse, which may include the extrapolation uncertainty from animal studies to human condition and the opposite effects (especially on cell proliferation) exerted by different peripheral estrogen metabolites.

A recent study which examined the downstream conversion of estrogens in synovial cells from patients with arthritis indicates that precursor estrogens are converted to proinflammatory metabolites, particularly in synovial cells of rheumatoid arthritis, and these cells mainly produce the proliferative agent (16 α OH-estrone) that does not inhibit TNF secretion (26). Specifically, HT or estrogen use has been shown to induce or exacerbate cutaneous inflammatory diseases such as contact allergy and eczema (27–29). Therefore,

estrogens are considered as enhancers of cell proliferation and humoral immune response in recent years (30, 31). Given the borderline association observed for current HT use and psoriasis risk in the present study, further investigation is needed to confirm the potential increased risk of psoriasis associated with hormone use.

Previous studies have found that psoriasis improves during pregnancy in women (12, 13). Our analysis found a suggestive lower psoriasis risk associated with multiple births and longer breast feeding duration in younger women, which is consistent with the literature on pregnancy and psoriasis. The improvement in psoriasis during pregnancy is found to be correlated with high estrogen levels but not progesterone levels (12). However, it is important to mention that during pregnancy several steroid hormones (e.g., cortisol, estrogens, and progesterone) increase. The role of cortisol as an anti-inflammatory hormone is well known. Nevertheless, a separate effect of one single steroid hormone is difficult to be isolated from that of other hormones in studies among pregnant women (24). In fact, proinflammatory Th-1 and Th-17 cytokines are up-regulated in psoriasis and play a key role in the inflammatory cascades of psoriasis, and it is likely that the Th-2 cytokine-mediated down-regulation of the immune response during pregnancy improves psoriasis by virtue of its anti-inflammatory and antagonizing effects on the Th-1 and Th-17 cytokines (3, 13). In addition, some women with psoriasis did not have improvement but experienced worsening or remained unchanged during pregnancy (12, 13). Therefore, further investigation is needed to clarify the complex association between pregnancy, parity and psoriasis.

In addition, we also found potential associations for menstrual cycle regularity in adulthood and surgical menopause and psoriasis risk. Hormonal fluctuations during the menstrual cycle modulate the immune function and progression of autoimmune diseases and other medical disorders (32, 33). The menstrual cycle might affect immune cell numbers and modulate their activity throughout the 4-week cycle. For example, regulatory T cells have been found to increase during the follicular phase of the menstrual cycle to reach its peak preovulatorily, while significantly decreasing in the following luteal phase (34). In addition, abrupt changes in the concentrations of circulating ovarian steroids at ovulation and premenstrually may account for menstrual cycle-related changes in chronic conditions such as menstrual migraine, epilepsy, asthma, rheumatoid arthritis, irritable bowel syndrome, and diabetes, which may be explained by baseline inflammation and immune cell activation in association with other mechanisms, such as regulation of receptor expression, modulation of muscular contraction and behavioral aspects (32, 33). It is plausible that irregularity of the menstrual cycle and surgical menopause may introduce disturbance on the above processes that lead to onset of psoriasis.

Our study has several strengths. First, we collected detailed, updated information on a variety of hormonal factors throughout the cohort follow-up, allowing for investigation of potential associations over long durations. Second, we were able to examine the association of psoriasis with different measures of endogenous and exogenous hormonal factors separately. Third, the study participants were all health professionals, and the accuracy of self-reported hormonal factors was likely to be high (35, 36). Finally, we were able to control for a number of known psoriasis risk factors and potential confounders based on the detailed follow-up information. Our study also has limitations. First, our study has retrospective characteristics given that information on psoriasis was asked at later time points in cohort follow-up. However, the recall on the examined health outcome (psoriasis) is expected to be highly accurate because over 90% of psoriasis self-reports were confirmed by PST which has 99% sensitivity and 94% specificity (37). Therefore, the potential misclassification of the health outcome is likely to be minimal. Second, although our participants could provide more accurate information on hormonal factors due to their health care background, exposure misclassification was inevitable given the self-report nature of the exposure information. Nevertheless, such misclassification was likely to be nondifferential given that exposure information was collected prospectively and thus may result in underestimated associations between exposures and health outcomes. Third, our study cohorts mostly comprised of white women, and the generalizability of the results to other ethnicities may be limited.

In conclusion, our study results suggest some potential associations between hormonal factors (e.g., irregularity of the menstrual cycle in adulthood and surgical menopause) and risk of psoriasis in women. However, no association reached statistical significance after Bonferroni correction for multiple comparisons, and further investigation is needed to clarify these potential associations. Nevertheless, our results provide the first comprehensive assessment for the relationship between hormonal factors and psoriasis in women, and may serve as the effort to initiate further research on this topic that may help advance the current medical knowledge on the modifiable risk profiles for psoriasis particularly in women.

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