Appendix S1

SUPPLEMENTAL MATERIAL AND METHODS

Study population

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. No exclusions were made on race when establishing the cohorts. However, the participants who entered the cohorts (nurses) were predominately white (95%). The occupational selections were made to increase the cost-effectiveness of the studies, and to improve internal validity of the collected health information drawing on the participants' health-care background. Information on risk factors and health data was updated by biennially mailed questionnaires in both cohorts. Follow-up rate has achieved over 90% during each biennial cycle (38). The institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health approved the study.

Assessment of hormonal factors

Endogenous hormonal factors. Age at menarche was asked at baseline in both cohorts. Menstrual regularity at an early life stage (ages 18–22) and in adulthood were asked in 1988 in the NHS I and in 1989 in the NHS II. On each questionnaire women were asked whether their menstrual periods have ceased permanently, at what age and for what reason (natural or surgical). Length of ovulatory life was calculated as the difference between age at natural menopause and age at menarche. At baseline, we collected data on parity, age at first birth, and histories of hysterectomy and oophorectomy, which were updated every 2 years thereafter. At each 2-year follow-up, we calculated age at last birth. We stopped asking participants in NHS I about parity and age at first birth in 1986 since the median age of the cohort was 47 years. Total months of breast feeding children was asked in 1986 in the NHS I and in 1997 in the NHS II.

Exogenous hormonal factors. Oral contraceptive (OC) and hormonal therapy (HT) use and duration of use in months were first asked at baseline (1976 in the NHS I and 1989 in the NHS II). At each 2-year follow-up, women were repeatedly asked whether they currently used OC and HT, number of months used during the past 24 months, and the type of hormones used. We then calculated total duration of use and time since last use at each 2-year follow-up. We stopped collecting OC information in 1984 in the NHS I when <1% of the premenopausal women were currently using the medication. Type of hormone was classified into 3 major categories for postmenopausal use: oral conjugated estrogen (E), combination oral conjugated estrogen plus progestin (E+P), and other hormones. Self-reported data on hormonal factors in the study participants are reported to have high reproducibility and accuracy (35, 36), and have been extensively used to investigate health conditions such as cardiovascular disease and inflammatory bowel disease (39, 40).

Assessment of covariates

Information on body weight and smoking was collected biennially through the follow-up. Height was assessed at baseline. Body mass index (BMI) was calculated as weight in kg divided by height in m². Alcohol intake was available in 1994, 1998,

2002, and 2006 in the NHS I and in 1991, 1995, 1999, and 2003 in the NHS II. Physical activity was assessed in 1996, 1998, 2000, and 2004 in the NHS I and in 1991, 1997, and 2001 in the NHS II. Information on histories of chronic diseases, including cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia, was also collected biennially through the follow-up.

Case ascertainment

In 2008, NHS I participants responded to an item on the questionnaire that asked about any history of clinician-diagnosed psoriasis and the date of diagnosis (1997 or before, 1998–2001, 2002–2005, 2006–2007, or 2008). In 2005, the NHS II participants were asked for personal history of clinician-diagnosed psoriasis and the date of diagnosis (before 1991, 1991–1994, 1995–1998, 1999–2002, or 2003–2005). A total of 2,475 NHS I participants and 2,586 NHS II participants reported having been diagnosed with psoriasis. Self-reported psoriasis was confirmed using the Psoriasis Screening Tool (PST) questionnaire, which inquires about the type of clinicians making the diagnosis and phenotypes (37). A pilot study using the PST showed 99% sensitivity and 94% specificity for psoriasis screening (37). We confirmed a total of 3,211 psoriasis diagnoses among 3,513 participants who returned the PST, with a confirmation rate of 91.4%. The overall prevalence of psoriasis in the study population is 2%, similar to the prevalence (1.5–3%) in the western population (1).

Statistical analysis

At baseline, we included women who returned the main questionnaires with psoriasis questions (see SFig. 1 for the derivation of the study participants). Women who reported psoriasis before baseline or not confirmed by the PST were excluded from the analysis, and women with a missing BMI at baseline were also excluded from the analysis given that high BMI is the major established risk factor for psoriasis (19). Person-years of follow-up for each participant were calculated from the return date of baseline questionnaire to the diagnosis date of psoriasis (assigned as the median of the reported diagnosis time period) or date of return of the last questionnaire (June 2008 in the NHS I and June 2005 in the NHS II), whichever came first. Cox proportional hazards analyses were used to estimate the age- and multivariate-adjusted hazard ratios
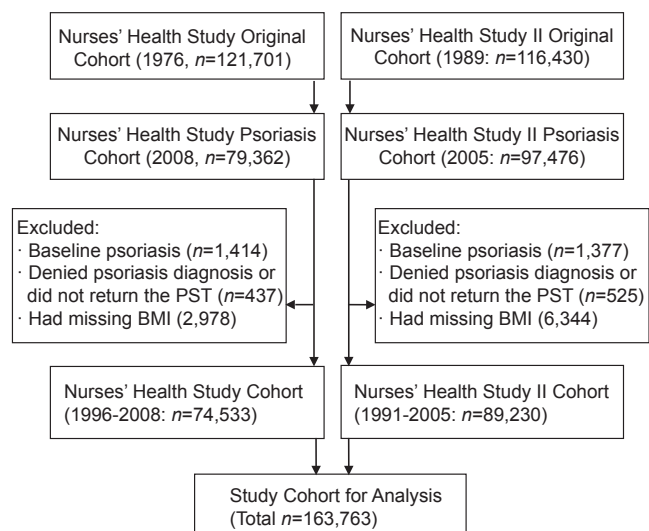
SFig. 1. Flow diagram of study participants.

(HRs) and 95% confidence intervals (CIs) of incident psoriasis associated with hormonal factors. Multivariate HRs were computed with adjustment for attained age, age at menarche, age at menopause, type of menopause, parity, HT use, OC use, BMI, alcohol intake, physical activity, smoking status, and personal histories of chronic diseases, including cardiovascular disease, type 2 diabetes, hypertension, and hypercholesterolemia. Covariates were selected based on previous literature from epidemiologic studies on psoriasis and associated risk factors and comorbidities (6, 15–19). Time-varying variables (e.g. BMI) were updated over the 2-year follow-up cycles to account for potential changes over the follow-up. To maintain the statistical power, we created an indicator for the missing data of a given variable when examining the associations of other variables with the health outcome (41). Trend tests were performed by treating exposure variables as continuous terms in the models. Analyses were conducted within each cohort separately and the results were pooled using a random-effect model. Heterogeneity test was performed with the use of Q statistic. We observed little heterogeneity in the association of hormonal factors with psoriasis risk between the two cohorts. Therefore, only pooled results were reported to simplify the presentation. All statistical analyses were conducted using Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc., Cary, NC). The Bonferroni correction for p-value was applied for multiple comparisons for individual hormonal factors, calculated as $0.05/n$ ($n = 16$). All statistical tests were 2-tailed, and the significance level was set at $p < 0.05$.