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Hypercholesterolemia and Risk of Incident Psoriasis and Psoriatic Arthritis in US Women

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Abstract

Objective—Psoriasis is a systemic inflammatory disorder associated with an increased risk of cardiovascular disease. Hypercholesterolemia is a major risk factor for cardiovascular disease, and patients with psoriasis or psoriatic arthritis (PsA) have been shown to have elevated cholesterol levels. However, whether hypercholesterolemia is associated with an increased risk of psoriasis or PsA is unknown. We aim to evaluate whether a history of hypercholesterolemia is associated with the risk of developing psoriasis and PsA in a cohort of US women.

Methods—A total of 95,540 participants were included from the Nurses' Health Study II (1991–2005). Information on personal history of physician-diagnosed hypercholesterolemia and related medication use was collected during the follow-up. Clinician-diagnosed psoriasis and PsA was ascertained and confirmed by supplementary questionnaires.

Results—During 1,320,765 person-years of follow-up, we documented 646 incident psoriasis and 165 concomitant PsA cases. Hypercholesterolemia was associated with an elevated risk of incident psoriasis [Hazard ratio (HR)=1.25, 95% confidence interval (CI): 1.04, 1.50] and PsA (HR=1.58, 95% CI: 1.13, 2.23) in multivariate adjusted models. Participants with hypercholesterolemia duration time ≥ 7 years were at a higher risk of developing psoriasis (HR=1.29, 95% CI: 1.03, 1.61) (P_{trend}=0.0002) and PsA (HR=1.68, 95% CI: 1.12, 2.52) (P_{trend}=0.002). These associations persisted among participants who never took cholesterol-lowering medications. There was no association between cholesterol-lowering drugs and risk of psoriasis or PsA.

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Competing interests
AAQ serves as a consultant for Abbott, Centocor, Novartis and the Centres for Disease Control and Prevention. The other authors state no conflict of interest.

Conclusions—Our study provides evidence that hypercholesterolemia, a well-known cardiovascular risk factor, is also associated with an elevated risk of psoriasis and PsA.

Keywords

hypercholesterolemia; inflammation; psoriasis; psoriatic arthritis

Psoriasis is a chronic inflammatory skin disease with involvement of the joints (psoriatic arthritis, PsA) in 10–40% of the cases (1–3). It is estimated that psoriasis affects 2–3% of the general population whereas PsA affects 520,000 individuals in the US population (1,4). Previous studies have demonstrated that psoriasis is associated with an increased risk of cardiovascular disease (5,6), and some common cardiovascular risk factors, such as obesity and smoking, have also been associated with increased risk of psoriasis and PsA in previous studies (7–10).

Hypercholesterolemia is the dominant risk factor that is associated with atherosclerosis in the United States and Europe (11), and has been associated with an increased risk of coronary heart disease (12), stroke (13), and myocardial infarction (14). Several previous cross-sectional and case-control studies have reported higher cholesterol levels among patients with psoriasis or PsA (15–17). However, the causal relationship between hypercholesterolemia and psoriasis/PsA is unclear. Hypercholesterolemia is able to induce microvascular inflammation with the involvement of immune system (18), and T lymphocytes may be one of the early cell types activated by hypercholesterolemia (19). Interestingly, psoriasis is characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes (20), and is classified as a T helper 1 (Th1) disease (21). To our knowledge, no prospective data on the association between hypercholesterolemia and psoriasis/PsA are available to date. To address the hypothesis, we investigated the association between a history of hypercholesterolemia and risk of incident psoriasis and PsA based on a large cohort of US women, the Nurses' Health Study II (NHS II). Furthermore, we also evaluated whether the magnitude of association varied by duration time of hypercholesterolemia and medication use for treatment of hypercholesterolemia.

METHODS

Study population

The NHS II was established in 1989 when 116,430 female registered nurses aged 25–42 years were enrolled using a mailed baseline questionnaire which inquired about medical history and lifestyle risk factors. Information on risk factors and health data was updated by biennially mailed questionnaires and a response rate exceeding 90% has been achieved during each follow-up cycle. The institutional review board of Partners Health Care System approved this study. The completion and return of the self-administered questionnaire was considered as informed consent.

Case ascertainment

In 2005, the 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). We

confirmed self-reported psoriasis using the Psoriasis Screening Tool (PST) questionnaire, which inquires about the type of clinicians making the diagnosis and phenotypes (22). A pilot study using the PST showed 99% sensitivity and 94% specificity for psoriasis screening (22). Diagnosis of psoriasis with concomitant PsA was confirmed using PsA screening and evaluation (PASE) questionnaire, which includes a symptom scale with seven items and a function scale with eight items (23). Participants chose one of five categories relating to agreement (strongly agree to strongly disagree) for each item. A total score of 47 or greater has been shown to identify PsA with high sensitivity (70%–82%) and specificity (73%–80%) in our pilot studies (23,24). PASE has good test–retest reliability and is sensitive to change with an individual's response to therapy (24). A recent study also reported a positive predictive value of 63% for PASE among psoriasis patients attending dermatology clinics (25). We sent out two waves of PST and PASE questionnaires to participants with self-reported disease during 2008–2011 and confirmed a total of 1,600 psoriasis cases, among which 348 were diagnosed with concomitant PsA. We excluded participants who self-reported psoriasis but did not respond to the PST or PASE questionnaire or were not confirmed (n=1,007), had prevalent psoriasis/PsA in 1991 (n=895), and confirmed to have psoriasis/PsA but with missing diagnosis date (n=34) from the data analysis.

Assessment of hypercholesterolemia

Personal history of physician-diagnosed hypercholesterolemia was assessed at 1989 and updated every 2 years thereafter. Self-reports of hypercholesterolemia were demonstrated to have high accuracy in the Nurses' Health Study, with 85.7% confirmed by medical records (26). Once a participant reported a diagnosis of hypercholesterolemia, she was considered to have a positive history of hypercholesterolemia until the end of the follow-up (27,28).

Assessment of cholesterol-lowering medication use

Participants were first inquired about the years of regular statins use (0–2 years, 3–5 years, and ≥7 years) in the 1999 questionnaire and were further inquired about regular statins use during the past two years in the 2001 and 2003 questionnaires. Regular use of other cholesterol-lowering drugs during the past two years was assessed in the 1999 and 2001 questionnaires.

Covariates

Information on weight, smoking, and personal histories of cardiovascular disease (myocardial infarction and stroke), type 2 diabetes and hypertension, was collected biennially since 1989. Height was reported in 1989. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared for each follow-up period. Alcohol intake was available in 1991, 1995, 1999, and 2003. Physical activity was assessed in 1991, 1997, 2001, and 2005. Information on menopausal status, postmenopausal hormones use and multi-vitamin use was also collected biennially during the follow-up whereas information on non-steroidal anti-inflammatory drugs (NSAIDs) use was first asked in 1989 and then collected biennially since 1993.

Statistical analysis

Person-years of follow-up for each participant were calculated from the return date of the baseline questionnaire (1991) to the date of diagnosis of psoriasis/PsA or the end of follow-up, whichever came first.

Cox proportional hazards analyses stratified by age and 2-year follow-up cycles were used to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between exposures and psoriasis/PsA. Time-varying variables were updated during the follow-up using the most recent data for each 2-year follow-up cycle. Multivariate-adjusted HRs for hypercholesterolemia were calculated after adjusting for age, BMI (<24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2), alcohol intake (0, <5, 5–9.9, or ≥10 g/d), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, or ≥27 metabolic equivalent hours/week), smoking status (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/day), cholesterol-lowering medication use (never, past, or current use), cardiovascular disease (yes or no), type 2 diabetes (yes or no), and hypertension (yes or no). As a sensitivity analysis, we also adjusted postmenopausal hormones use (premenopausal, never, past, or current use), NSAIDs use (never, past or current use), and multi-vitamins use (never, past, or current use) in the models. We evaluated the influence of duration of hypercholesterolemia on outcome diseases by comparing to those without hypercholesterolemia. We set 7 years as the cut point because we had a follow-up of 14 years. Trend tests for duration of hypercholesterolemia were performed using hypercholesterolemia lasting time as a continuous variable.

Secondary analyses were carried out after excluding individuals with baseline histories of cardiovascular disease, type 2 diabetes and hypertension. 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

We included 95,540 participants from the NHS II, and confirmed 646 incident psoriasis cases during 1,320,765 person-years of follow-up. Of these psoriasis cases, 165 were diagnosed with concomitant PsA. The median ages for diagnoses of incident psoriasis and PsA were 44 years and 47 years, respectively. Baseline characteristics of the study participants are shown in Table 1. Participants with a history of hypercholesterolemia tended to have a higher mean BMI and higher proportions of current smoking, cardiovascular disease, type 2 diabetes, and hypertension, and were less physically active than those without hypercholesterolemia.

Hypercholesterolemia was associated with an elevated risk of incident psoriasis (age-adjusted HR=1.49, 95% CI: 1.26, 1.77) or psoriasis with concomitant PsA (age-adjusted HR=2.14, 95% CI: 1.55, 2.94) (Table 2). These associations attenuated in multivariate models adjusted for BMI, alcohol intake, physical activity, smoking status, and cholesterol-lowering medication use. Further adjustment for cardiovascular disease, type 2 diabetes and hypertension did not change the risk estimates materially. The fully adjusted HRs of incident psoriasis and PsA associated with hypercholesterolemia were 1.25 (95% CI: 1.04, 1.50) and

1.58 (95% CI: 1.13, 2.23), respectively. Participants with hypercholesterolemia duration time ≥ 7 years were at a higher risk to develop psoriasis (fully adjusted HR=1.29, 95% CI: 1.03, 1.61) (P_{trend}=0.0002) and PsA (fully adjusted HR=1.68, 95% CI: 1.12, 2.52) (P_{trend}=0.002).

We stratified the analyses by regular medication use status in hypercholesterolemic participants, and found similar increased risk of incident psoriasis and PsA among hypercholesterolemic participants with no medication. The fully adjusted HRs were 1.26 (95% CI: 1.05, 1.51) for psoriasis and 1.62 (95% CI: 1.15, 2.27) for PsA among hypercholesterolemic participants with no medication (Table 3). We further stratified the analyses by regular medication use status among all participants, and there was no association between medication use and psoriasis and PsA (supplemental Table S1).

We performed sensitivity analyses with additional adjustment for postmenopausal hormones use, multi-vitamins use and NSAIDs sue, and the associations were only slightly attenuated (data available upon request). Secondary analyses after excluding individuals with baseline histories of cardiovascular disease, type 2 diabetes and hypertension did not appreciably change the results and the magnitude of effects appeared similar (data available upon request).

DISCUSSION

Our study examined the association of hypercholesterolemia with incident psoriasis and psoriasis with concomitant PsA for the first time in a large cohort of US women. After adjusting for a number of potential confounders, we found that a history of hypercholesterolemia was associated an increased risk of incident psoriasis and PsA. The associations between hypercholesterolemia and psoriasis and PsA among participants with no cholesterol-lowering medication were almost equal to those among all participants, suggesting an effect of hypercholesterolemia on incident psoriasis and PsA that is independent of cholesterol-lowering medication use. In particular, the risk of incident psoriasis and PsA was stronger among participants with long-term duration (≥ 7 years) of hypercholesterolemia (P_{trend}<0.01). These results suggest that hypercholesterolemia, as a well-known risk factor of cardiovascular disease, may also increase the risk of incident psoriasis/PsA.

Psoriasis is a disease characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes and is classified as a T helper 1 (Th1) disease, whereas PsA tends to have more severe skin phenotypes with involvement of the joints (1,20,21). Many previous studies have demonstrated that individuals with psoriasis or PsA are prone to have a distinct cluster of concomitant conditions known as metabolic syndrome, among which hypercholesterolemia is an important component (15,29–32). It has been proposed that hypercholesterolemia can convert the normal anti-inflammatory phenotype of the microcirculation to a proinflammatory phenotype, which may result from an increased generation of reactive oxygen species (ROS) and a decline in bioavailability of nitric oxide (NO) (11). Both generation of ROS and decline in NO bioavailability are important in the development of atherosclerosis (33), and both hypercholesterolemia and inflammation are

shown to be involved in the pathogensis of atherosclerosis (34,35). Furthermore, hypercholesterolemia is able to induce microvascular inflammation with the involvement of immune system (18), and it has been established that both innate and adaptive immune systems participate in the responses of postcapillary venules, and possibly arterioles, to elevated cholesterol levels, and that T lymphocytes may be one of the early cell types activated by hypercholesterolemia (19). Therefore, hypercholesterolemia may increase the risk of psoriasis through inflammatory pathways with involvement of the immune system.

As one of the essential precursors of atherosclerosis, hypercholesterolemia was more frequently found in patients with psoriasis/PsA than in controls in previous population-based studies (15–17). However, the temporal relationship between hypercholesterolemia and psoriasis/PsA is unclear given the cross-sectional or case-control nature of previous studies. Our findings therefore provide prospective evidence that hypercholesterolemia is associated with an increased risk of psoriasis and PsA. Participants with long-term duration of hypercholesterolemia more than 7 years were more likely to develop psoriasis and PsA, which is consistent with the concept that psoriasis is associated with a chronic inflammatory state (1).

Previous studies have documented that prescriptions of certain drugs may increase psoriasis risk or make it more severe (36–38). In contrast, statins are postulated to have anti-inflammatory and immunomodulatory effects (39), and a recent large case-control study found a reduced risk of psoriasis associated with current short-term statins use (last prescription <30 days before index date) but not with long-term statins use (40). Our results are consistent with the previous case-control study by Brauchli et al. (40) which do not support the hypothesis that long-term statins use may substantially decrease the risk of developing psoriasis (41). Nevertheless, evidence for the relationship between cholesterol-lowering drugs and psoriasis/PsA risk is rare and further research is needed to address whether there is any causality and the underlying biological mechanisms.

Our study has retrospective characteristics and selection and information bias may be a concern. However, our participants were all young health care professionals and their reports on both cardiovascular risk factors and psoriasis were previously demonstrated to be of high accuracy (22,26). In particular, psoriasis self-reports have reached a confirmation rate of 92% (22). Furthermore, we compared the characteristics of participants who responded to psoriasis questions with those who did not respond, and found that the main characteristics (e.g., BMI, smoking, and alcohol intake) were similar between responders and non-responders (42). Therefore, it is less likely that our results would differ greatly due to response bias. Second, one recent study indicated a lower sensitivity of PASE (25) while another documented a lower specificity of PASE (43), raising the concern about possible misclassification of PsA cases. PASE picks up individuals with active disease who are potentially more likely to have inflamed joints and increased systemic inflammation, and therefore it probably underestimates the number of cases. However, we sent out two waves of validation questionnaires to participants with self-reported disease. In the second wave of PASE questionnaires we added an enquiry ‘Has a rheumatologist ever diagnosed you with psoriatic arthritis?‘, and later on validation was based on answer to the enquiry as well as other items of PASE. Results showed good consistency between the rheumatologist’s

diagnosis and our previous criteria (score cutoff of 47), with a sensitivity of 77% and a specificity of 79%. Third, we were not able to assess the risk of psoriasis or PsA associated with other lipid metabolic disorders (e.g., hypertriglyceridemia and hyperlipoproteinemia) in the present study. These disorders are correlated with each other and form the hyperlipidemia jointly, and therefore we would expect to find similar increased risk of psoriasis/PsA associated with other forms of hyperlipidemia (16). Nevertheless, further research is needed to clarify this issue. Third, our participants were exclusively of women, most of which were whites, and thus may limit the generalizability of the results to other gender and ethnicities.

In conclusion, our findings suggest that hypercholesterolemia, a well-known risk factor of cardiovascular disease, is also associated an elevated risk of incident psoriasis and PsA. Further work is needed to investigate the underlying mechanisms behind these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics[a] of the study participants in the NHS II (1991–2005) according to hypercholesterolemia

	Hypercholesterolemia	
	No N=81,808	**Yes N=13,732**
Age, years, mean (SD)	36.0 (4.6)	37.2 (4.7)
White, %	95.4	94.3
BMI, kg/m^2, mean (SD)	24.2 (5.0)	26.2 (6.1)
Alcohol intake, g/d, mean (SD)	3.2 (6.1)	2.9 (6.1)
Physical activity, metabolic equivalent hrs/wk, mean (SD)	21.0 (27.0)	19.4 (25.4)
Current smoking, %	11.3	12.8
Cardiovascular disease, %	0.02	0.06
Type 2 diabetes, %	0.1	0.4
Hypertension, %	5.1	12.9
Current postmenopausal hormones use, %	2.2	4.2
Current non-steroidal anti-inflammatory drugs use, %	22.9	29.4
Current multi-vitamins use, %	38.6	39.1

[a]Other than age, all variables are standardized to the age distribution of the study participants

Table 2

Hazard ratios of incident psoriasis and PsA according to hypercholesterolemia

	Cases	Person-Years[a]	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[b] (95% CI)	Multivariate-adjusted HR[c] (95% CI)
Psoriasis					
No hypercholesterolemia	427	1,006,906	1.00	1.00	1.00
Hypercholesterolemia	219	313,859	1.49 (1.26, 1.77)	1.26 (1.06, 1.51)	1.25 (1.04, 1.50)
Duration of hypercholesterolemia < 7 years	87	147,630	1.41 (1.12, 1.78)	1.22 (0.96, 1.55)	1.20 (0.95, 1.53)
Duration of hypercholesterolemia ≥ 7 years	132	166,230	1.56 (1.27, 1.92)	1.30 (1.05, 1.62)	1.29 (1.03, 1.61)
P_{trend}			<0.0001	<0.0001	0.0002
Psoriasis with concomitant PsA					
No hypercholesterolemia	93	1,002,575	1.00		1.00
Hypercholesterolemia	72	312,458	2.14 (1.55, 2.94)	1.60 (1.14, 2.24)	1.58 (1.13, 2.23)
Duration of hypercholesterolemia < 7 years	28	146,892	1.93 (1.26, 2.96)	1.50 (0.97, 2.31)	1.48 (0.96, 2.29)
Duration of hypercholesterolemia ≥ 7 years	44	165,566	2.31 (1.58, 3.39)	1.69 (1.13, 2.54)	1.68 (1.12, 2.52)
P_{trend}			<0.0001	0.002	0.002

[a] Person-years of hypercholesterolemia duration < 7 years and ≥ 7 years for psoriasis did not add up to total hypercholesterolemia person-years because of rounding.

[b] Simultaneously adjusted for age, BMI (<24.9, 25–29.9, 30–34.9, and ≥35 kg/m^2), alcohol intake (no, <5.0, 5.0–9.9 or ≥10.0 g/d), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9 or ≥27.0 metabolic equivalent hours/week), smoking status (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/day), and cholesterol-lowering medication use (statins and others) (never, past or current use).

[c] Additionally adjusted for cardiovascular disease (yes or no), type 2 diabetes (yes or no), and hypertension (yes or no).

Table 3

Hazard ratios of incident psoriasis and PsA according to hypercholesterolemia with and without related medication use

	Cases	Person-Years[a]	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[b] (95% CI)	Multivariate-adjusted HR[c] (95% CI)
Psoriasis					
No hypercholesterolemia	427	1,006,906	1.00	1.00	1.00
Hypercholesterolemia with no medication	180	276,817	1.45 (1.21, 1.73)	1.28 (1.07, 1.53)	1.26 (1.05, 1.51)
Hypercholesterolemia with regular statins use	36	34,805	1.75 (1.22, 2.50)	1.36 (0.95, 1.95)	1.21 (0.83, 1.76)
Hypercholesterolemia with regular other cholesterol-lowering drugs use	7	4,361	2.62 (1.23, 5.57)	2.05 (0.96, 4.38)	1.78 (0.83, 3.83)
Psoriasis with concomitant PsA					
No hypercholesterolemia	93	1,002,575	1.00	1.00	1.00
Hypercholesterolemia with no medication	60	275,541	2.11 (1.52, 2.95)	1.64 (1.17, 2.29)	1.62 (1.15, 2.27)
Hypercholesterolemia with regular statins use	11	34,687	2.22 (1.15, 4.30)	1.40 (0.72, 2.72)	1.23 (0.62, 2.44)
Hypercholesterolemia with regular other cholesterol-lowering drugs use	2	4,351	3.21 (0.78, 13.2)	1.94 (0.47, 8.03)	1.65 (0.39, 6.95)

[a] Person-years of hypercholesterolemia with no medication, statins use, and other cholesterol-lowering drugs use did not add up to total hypercholesterolemia person-years because a small proportion of participants used statins and other drugs simultaneously.

[b] Simultaneously adjusted for age, BMI (<24.9, 25–29.9, 30–34.9, and ≥35 kg/m^2), alcohol intake (no, <5.0, 5.0–9.9 or ≥10.0 g/d), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9 or ≥27.0 metabolic equivalent hours/week), and smoking status (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/day).

[c] Additionally adjusted for cardiovascular disease (yes or no), type 2 diabetes (yes or no), and hypertension (yes or no).