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Identification of Risk Factors for Psoriatic Arthritis: Scientific Opportunity Meets Clinical Need

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Psoriatic Arthritis (PsA) is a chronic inflammatory disease that can be progressive and may be associated with permanent joint damage and disability. Though rare in the general population, it is common in patients with psoriasis, affecting about 6–10% of psoriasis patients over all with significantly higher estimates (20–40%) in patients with more extensive skin disease[1, 2]. In most patients with PsA, the symptoms do not develop until years after the onset of cutaneous psoriasis. As a result, patients with psoriasis (Ps) represent a unique opportunity to identify individuals at very high risk of developing a chronic inflammatory arthropathy (i.e. PsA). In order to determine which patients with psoriasis are at greatest risk of developing PsA it is essential that risk factors be identified using robust epidemiological approaches.

Risk factors are important to identify because they may be in the causal pathway of an association, and, if modifiable, could present an opportunity for prevention. A risk factor is associated with the odds of developing a disease and this association is not due to an indirect association (e.g. confounding) or systematic error in the study design (e.g. bias). Risk factors are typically classified as either non-modifiable (i.e. genetic) or modifiable (i.e. environmental), although in many cases, both a genetic and environmental exposure may be necessary to produce a disease. The importance of risk factor identification is well demonstrated in the field of cardiology where over sixty risk factors for cardiovascular disease have been identified since 1951[3]. In comparison, epidemiological studies evaluating risk factors for psoriatic disease did not start until the current decade and very few environmental risk factors (such as obesity and smoking for psoriasis) have been identified and confirmed in more than one study. Furthermore, it is not known if modification of risk factors for psoriasis will result in prevention of the disease or modification of the severity of its presentation. Similarly, few studies have examined risk factors for developing PsA among psoriasis patients. Given that joint damage and functional impairment could be

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potentially be prevented by modification of risk factors and by early identification of these patients, knowledge about PsA risk factors is especially important.

In studying risk factors for a rare disease, the most commonly employed design is the case-control study in which patients are identified by disease status. Case-control studies have made major public health advances by identifying risk factors for diseases such as cancer (e.g. smoking and lung cancer, sun burns and melanoma)[4, 5]. Ideally incident cases are identified in order to ensure that exposure factors truly preceded disease onset. This is especially challenging in PsA because early symptoms may be non-specific, patients may delay seeking medical care, and there are no gold standard objective criteria for this disease. Furthermore, five clinical presentations of PsA and frequent confusion with other common arthropathies such as osteoarthritis make diagnosis challenging[6]. Case definitions used in epidemiological studies of PsA range from patient self-report of a physician diagnosis of PsA, to a documented rheumatologist clinical diagnosis of PsA to the use of diagnostic criteria such as CASPAR (ClASsification of Psoriatic ARthritis) and Moll and Wright criteria[7 8, 9]. In order to identify risk factors, cases and controls, the later defined as those without disease at the time the case patient is identified, are selected (ideally) from the same source population in order to minimize selection bias. Furthermore, case-control studies are ideally nested within cohort studies in which exposure factors are measured prospectively in order to minimize information bias (e.g. cases may recall exposures differently than those without disease).

Genetic risk factors for PsA have been studied in several case-control genome wide association studies. Genetic studies have been motivated by the observation that patients who had a family history of PsA were 27–48 times more likely to develop this disease than controls[10, 11], making PsA more highly heritable than other autoimmune diseases[12]. Studies of genetic risk factors have the advantage being robust to recall bias; and, studying a fixed exposure such as genotype ensures that the exposure (e.g. one's genotype) preceded the onset of the disease. Validity could be threatened however by the accuracy of the case definition and the representativeness of cases and controls of the source population from which they are derived. These studies are additionally limited by the possibility that the variation marked with the strongest association may be in high correlation, or linkage disequilibrium, with the true common variation of interest mark[13]. Many genes implicated in PsA susceptibility are shared with psoriasis susceptibility genes such as HLA-Cw*0602, HLA-B27 (though specifically associated with axial involvement in PsA), HLA-B38 and HLA-B39 (though more specifically with peripheral polyarticular involvement), TNF*-238A, TNIP1, IL23R and IL12R, and HLA-DR4. However, not all genes have been shown to promote both diseases. For example, the following associations have been published: TNFAIP3 (Ps only), corneodesmosin or CDSN (Ps only), HCR (Ps only), a SNP between SLC9A3R1 and NAT9 associated with loss of the RUNX1 binding site (Ps only), TNF-857 (PsA only), KIR2DS1 (PsA), HLA-Cw*1203 (PsA), and HLA-DRB1 (`shared epitope' in rheumatoid arthritis, is correlated with erosions in PsA)[11, 12, 14–20]. Larger studies adequately characterizing the psoriatic phenotype and using more sophisticated sequencing techniques are likely to shed more light on the genetic risk factors for psoriasis and psoriatic arthritis, especially as it pertains to the phenomenon of linkage disequilibrium with other genes[21].

In addition to genetic risk factors, several studies have examined modifiable risk factors for PsA (Table 1). Thumboo et al conducted the first study nested in a psoriasis cohort in Olmstead county[22, 23]. They found that prior use of oral steroids increased the risk of PsA whereas pregnancy was protective (e.g. lowered the risk of PsA). These results have not been confirmed by further studies. The finding of corticosteroid use as a risk factor for PsA is especially difficult to interpret given the strong possibility of confounding by indication.

Several years later, Wilson et al used the same database and a similar design[24]. In both univariate and multivariate models, the risk factors identified included Ps involving the scalp and intergluteal/perianal region, involvement of more than 3 sites, and nail dystrophy. Some of these clinical risk factors may be surrogates however, for more severe psoriasis leading to an increased risk of PsA.

Pattison et al also used a case-control study to ascertain risk factors for PsA[25]. Notably, the Ps and PsA cases were taken from different source populations: PsA cases were recruited by referral from their rheumatologist or from a media campaign while psoriasis patients were recruited as controls from a dermatology psoriasis clinic. While many risk factors were examined, only a few were significant (see Table 1). The use of two differing source populations introduces selection bias, however, making the results difficult to interpret. For example, the controls had more severe psoriasis than the cases, suggesting that more severe psoriasis is protective of developing PsA, though this could be attributed to selection bias introduced by sampling the controls from a dermatology clinic, a different source population from which the cases were derived.

In this issue of the *Archives*, Soltani-Arabshahi et al present results from a case-control study in their dermatology population[26]. Risk factors for the development of PsA in Ps patients included patient reported body mass index (BMI) at the age of 18 (though current BMI was not predictive), nail involvement, patient reported Koebner phenonomenon, female gender, younger age of psoriasis onset, and self reported worst body surface area ever covered with psoriasis(Table 1). Importantly, the limitations of this study include the case definition of PsA, difficulty establishing a temporal relationship the factors evaluated, and the lack of validation data on the accuracy of patient recall of BMI at age 18. Furthermore, it is likely that some cases of PsA were actually osteoarthritis (OA), a common joint disease easily confused with PsA[6]. Female sex and obesity are risk factors for OA and therefore misclassification bias in the ascertainment of the cases may have influenced the results[27–30].

With the exception of severity of skin psoriasis, the existing studies of risk factors for PsA have yielded generally inconsistent findings. These inconsistencies are potentially related to systematic error (e.g. bias in the study design) or variations in populations studied (e.g. the findings are valid but not generalizable). Prospective data collection may have the advantage of identifying truly incident, well defined, cases of PsA with controls selected from the same population. Such a study to observe for the development of PsA was recently initiated in 2006. The incidence of PsA in the first year was 4.3% and family history of PsA and nail dystrophy were most predictive of PsA development[31]. Through data accrued in the coming years, we eagerly await future risk factor studies which may overcome the methodological challenges of previous investigations. Ultimately, identification of risk factors for PsA holds the promise of improving our ability to diagnose this condition and preventing it through risk factor modification.

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Table_ Epidemiological Studies of Risk Factors for PsA

Study	Study Design	Source Population	PsA Case Definition	Data Source(s)	Significant Findings (with 95% CI)
Thumboo 2002	Population-based Retrospective Nested Case-Control	Dermatologist Diagnosed Psoriasis patients identified in the medical records database	Ps with inflammatory arthritis Cases N=60 Controls N=120	Rochester Epidemiology Project Database and Self-Administered Questionnaires	Corticosteroid Use in 2 yrs prior to Ps onset: OR 4.33 (CI 1.34–14.02) Pregnancy in 2 yrs prior to Ps onset: OR 0.19 (CI 0.05–0.95)
Wilson 2009	Population-based Retrospective Nested Case-Control	Incident dermatologist diagnosed psoriasis patients identified in the medical records database	CASPAR Criteria* Cases N=97 Controls N=1593	Rochester Epidemiology Project Database	Ps involving the scalp: HR 3.89 (CI 2.18–6.94) Ps involving intergluteal/ perianal: HR 2.35 (CI 1.32–4.19) Ps involving > 3 affected sites: HR 2.24 (CI 1.23–4.08) Nail dystrophy: HR 2.93 (CI 1.68–5.12)
Pattison 2008	Clinic-based retrospective Case-Control	Controls selected from a dermatology psoriasis clinic. PsA patients recruited from rheumatology clinic and media campaign	Rheumatologist Diagnosis Cases N=98 Controls N=163	Self-administered Questionnaires	Trauma leading to medical care: OR 2.53 (CI 1.1–6.0) Vaccination for rubella: OR 12.4 (CI 1.2–122.14) Moving to a new home: OR 2.29 (CI 1.21–4.4) Treatment for fertility problems: OR 0.17 (CI 0.04–0.79)
Soltani-Arabshahi 2010	Clinic-based retrospective Case-Control	Dermatology Psoriasis Clinic.	Patient Report of a Rheumatologist Diagnosis Cases N=250 Controls N=693	Utah Psoriasis Initiative Database and Self-administered Questionnaires	Patient reported body mass index (BMI) at the age of 18: HR 1.06 (CI 1.02–1.10) Nail involvement: OR 1.76 (CI 1.25–2.47) Patient reported Koebner phenomenon: OR 1.59 (CI 1.17–2.14) Female gender: OR 1.45 (CI 1.09–1.94) Age of psoriasis onset: OR 0.98 (CI 0.96–0.98) Self-reported worse body surface area ever covered with psoriasis: OR 1.01 (CI 1.00–1.01)

* The CASPAR criteria classifies PsA as an inflammatory arthritis in addition to three of the five following features: 1) Current or personal history of psoriasis or a family history of Ps in a first or second degree relative, 2) Psoriatic nail dystropahy, 3) negative rheumatoid factor, 4) dactylitis (current or history recorded by a rheumatologist), and 5) radiographical evidence of juxtaarticular new bone formation excluding osteophytic formation.[8–9]