Curr Derm Rep (2013) 2:58–65
DOI 10.1007/s13671-012-0034-6

EPIDEMIOLOGY (J GELFAND, SECTION EDITOR)

Risk Factors for Psoriasis

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Published online: 11 January 2013

Abstract Multifactorial heredity, involving interaction between genetic and environmental factors, is the model hypothesized for psoriasis causation. Measures of heritability indicate that from 50 % to 90 % of the psoriatic phenotype is connected with genetic factors. The remaining variability is due to environmental factors. Candidate risk factors can be initially identified by analyzing variations in population incidence or prevalence. A trend toward increasing incidence of psoriasis in recent decades has been documented. Analytic epidemiologic studies offer a better insight into risk factors allowing to obtain quantitative estimates of the contribution of a factor of interest to the disease and to control for potential confounders. Smoking habits, alcohol consumption, diet, obesity, physical inactivity, infection, drugs, and stressful life events have been considered as candidate risk factors. Convincing proofs exist for only a few of them, namely smoking and obesity. Knowledge of potentially avoidable risk factors may offer clues to plan preventive measures.

Keywords Psoriasis · Epidemiology · Incidence · Risk factors · Smoking · Obesity · Prognosis

Why Study Risk Factors?

In epidemiology, a "*risk factor*" (sometimes referred to also as a "*determinant*") is a variable associated with an increased risk or probability of developing a disease. Similarly, a "protective factor" acts by reducing the disease risk. The term "risk factor" was first coined by William B. Kannel, former Framingham Heart Study Director, in 1961 [1]. The concept implies a complex model of disease causation where the occurrence of a disease depends on interplay between multiple associated variables that could be measured by the extent to which they affect the probability of disease occurrence. Hints on the role of environmental risk factors can be provided by simple descriptive epidemiology studies (e.g., ecological correlations); however, risk confirmation and quantitative estimates could only be obtained by analytic epidemiology studies, i.e., cohort and case-control studies. Cohort studies are studies where groups are defined according to the exposure status (e.g., smokers vs. nonsmokers) and are followed up with subsequent events (e.g., psoriasis) being recorded and compared. On the contrary, case-control studies are studies where groups are defined according to their experience of an outcome of interest (e.g., newly diagnosed psoriasis patients and their neighbor controls) and prior exposures are ascertained retrospectively and compared. The association of an exposure with a given event is usually expressed in terms of a "relative risk," "hazard ratio" (a measure of risk in survival analyses), or "odds ratio" (an estimate of the relative risk obtained from case-control studies). The relative risk is a measure of the size of an association in relative terms. It refers to the ratio of the incidence of the outcome among exposed individuals to that among nonexposed. Values greater than 1 represent an increase in risk associated with the exposure, whereas values less than 1 represent a reduction in risk. A relative risk of two, for example, tells us that the event under study occurs two times more often in the exposed people than in nonexposed. When performing epidemiologic studies to evaluate one or more determinants for a specific disease, the other determinants may act as so-called "confounding factors" (or "confounders") and need to be controlled for, e.g., by stratification or multivariate analysis. Potential confounders vary with what outcome is studied, but some general confounders, such as age

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and gender, are common to most epidemiological associations and are the determinants which should be regularly controlled for in epidemiological studies.

Statistical analysis alone is usually not sufficient to establish disease determinants. The Bradford Hill criteria have been proposed as a group of minimal conditions necessary to provide adequate evidence of a causal relationship. They include the strength of the association (e.g., size of the relative risk), consistency, specificity, temporal relationship, biological gradient (e.g., dose-response relationship), biological plausibility, coherence, and further experimental evidence [2].

Multifactorial heredity, i.e., interaction between genetic predisposition and environmental factors, is the model hypothesized for the causation of several chronic inflammatory disorders, including psoriasis. According to the model, the susceptibility to psoriatic lesions depends on both genetic and extra-genetic predisposing factors and is shared by the whole skin. Disease expression, in terms of visible lesions, is modulated by extra-genetic precipitating or initiating factors. Knowledge of avoidable environmental factors may offer clues to plan preventive measures. In addition, environmental influences should be carefully considered in genetic studies, because they can modify the association with genetic markers.

Hints on Risk Factors from Descriptive Epidemiology

Candidate risk factors can be first identified by analyzing variations in population incidence or prevalence measures. A special case of these analyses are *ecological correlations*, which explore the relationship between two variables that are group means rather than measures that describe individuals. For example, one might study the correlation between average population consumption of fish and incidence or prevalence of psoriasis in different geographic areas or ethnic groups. Unfortunately, the limitation of data concerning the incidence or prevalence of psoriasis hampers most of these exploratory analyses [3].

Ethnic and Geographic Variations

Geographic and ethnic variations are observed for psoriasis. Mongoloid races in the Far East of Asia have remarkably low prevalence rates [4••]. Lower prevalence rates have been also documented in African Americans compared with Caucasians in United States [5•]. Duffy et al. [6], analyzing cumulative incidence in 3,808 twin pairs, documented significantly higher prevalence rates in southern states of Australia with respect to northern areas. Geographical variations were also described by Braathen et al. [7] with the northern regions of Troms and Finmark showing higher rates and Hedmark and Oppland regions in the south of the country showing lower rates.

Sex, Age, and Time Variations

Most prevalence studies suggest that psoriasis tends to be slightly more prevalent among men compared with women. The few studies available that provide age-specific incidence rates of psoriasis suggest that incidence increases more or less steadily with age up to the seventh decade of life. If psoriasis appeared throughout life, then both point prevalence and lifetime prevalence would increase with age. However, prevalence estimates in several studies do not increase with age and even decreases [6–8], suggesting higher mortality rates in older patients with psoriasis compared with the general population. Age variations in morbidity are expected for many diseases and their biological basis are generally complex [9]. A small proportion of common chronic disorders may be due to simple Mendelian mechanisms, and they typically manifest at an earlier age compared with the usual type. Age-at-onset distribution may be employed to test hypotheses about etiologic factors. Evidence of bimodality suggests etiologic heterogeneity and lognormal distribution (Sartwell's model) [9, 10] a single-gene disorder (age-at-onset for genetic disorders is the equivalent of the incubation period in infectious diseases). In the past, much emphasis has been placed on age-at-onset in discriminating between different types of psoriasis. It has been reported that age-at-onset in large series of psoriatic patients has a bimodal distribution [11]. This has been taken as evidence for etiologic heterogeneity and type I and type II psoriasis have been proposed. Patients with onset of psoriasis before age 40 years (type I psoriasis) are much more likely than patients with onset after age 40 years (type II psoriasis) to have affected first-degree relatives, to express susceptibility alleles at the HLA locus, and to experience severe and recurrent disease. This is an interesting concept. However, aside from study design issues, such as case definition and selection (e.g., the selection of juvenile cases may conditioned by their family history more frequently than cases in the older age groups), a fundamental problem in these analyses arises from the fact that the numerical distribution by age of cases of psoriasis is a function of the age-specific disease rate and the age distribution of the population. That is, variations in numerator data, i.e., the number of people experiencing onset at different ages, may simply reflect the age distribution of the population of origin. In my opinion, age-specific rates of appearance of psoriasis calculated on representative samples of the general population would be more convincing. A trend of increasing incidence during a 30-year period, between 1970 and 2000, has been recently documented for both adult-onset psoriasis and psoriatic arthritis in studies

from the Olmsted County, Minnesota [12••, 13••]. This increasing trend may reflect a variety of factors, including a true change in risk factors (e.g., obesity) or changes in the diagnosing patterns. Incidence in males displayed a slightly bimodal pattern but this was not significant. Among female subjects, a prominent increase in incidence in the sixth decade of life that corresponds to the post-menopausal period was documented.

Familial Aggregation

A history of psoriasis in first-degree relatives is given by 20-30 % of patients with psoriasis. In a study, the prevalence of psoriasis increased with the number of first-degree relatives affected from 3 % with no relative affected, to approximately 40 % with two relatives affected [8].

Risk Estimates from Analytic Epidemiology

Genetic Factors

The role of genetic factors is well established. Their review is outside the scope of this chapter. *Heritability* quantifies the overall role of genetic factors when a multifactorial model of inheritance is postulated, i.e., phenotype is a linear function of independent genetic and environmental factors. When the phenotype is discrete (i.e., affected versus non-affected), the statistical model assumes that an underlying continuous trait (termed "liability") dictates risk of disease. Heritability is a ratio and its measures lie between 0 and 1.0. Measures of the heritability of psoriasis have been provided based on population data and the analysis of concordance of twins. The estimates ranged from 0.5 to 0.9 [6, 8, 14], indicating that from 50 % to 90 % of the psoriatic phenotype is connected with genetic factors. The highest estimates come from twin studies. Twins are uniquely matched for genetic factors, and they provide an upper estimate of heritability. For comparison, heritability estimates of rheumatoid arthritis range from 0.5 to 0.65.

Genome-wide association studies (GWAS) have contributed to the discovery of many susceptibility variants. However, a large proportion of the heritability still remained unexplained. The "missing heritability" is probably hidden in the genome among the large number of variants with small effects [15].

Smoking and Alcohol Consumption

Smoking has been consistently linked with psoriasis. Studies that examined the exposure before the onset of psoriasis and control for confounding factors offer the more convincing evidence (Table 1) [16•, 17••, 18••, 19•, 20••]. In a combined analysis of three large cohorts in the United States, there was a trend toward an increased risk of psoriasis with increasing pack-years or duration of smoking. In addition, there was a graded reduction of risk with an increase in time since smoking cessation [20••]. Genetic-environmental interaction involving smoking also has been proposed even if not well documented by a few studies of psoriasis. In a study, a stronger association between smoking and psoriasis in subjects with nonvariant CYP1A1 genotype was presented, suggesting that sequence variation in genes coding for phase 1 and phase II enzymes, including members of cytochrome P450 (CYP) family, may alter individual susceptibility to developing psoriasis in smokers, similarly to the documented effects in cancer and coronary artery disease [21]. In another study from a Chinese group, the risk of psoriasis for smokers with HLA-Cw6 increased approximately 11-fold than nonsmokers without HLA-Cw6 [22]. In an additional study, evidence was presented that polymorphisms in the *IL13/IL4* region (especially rs1800925*T) may associate with protection from developing psoriatic arthritis and that this effect may be abrogated by smoking. It was unclear, from the data presented, whether smoking *per se* was associated with psoriatic arthritis [23•]. Cigarette smoking is a complex risk factor that involves a cocktail of more than 4,000 chemicals [24]. Nicotine is the principal alkaloid in tobacco. It exerts its effects by activating various subtypes of nicotinic acetylcholine receptors (nAChRs), which are classically found in the nervous system and adrenal medulla but also have been identified in nonneuronal tissue, such as skin keratinocytes; nAChRs facilitate cell-to-cell communication, keratinocyte adhesion, and upward migration in the epidermis. Components of tobacco smoking other than nicotine, such as acrolein, benzo(a)pyrene, or hydroquinone, also may exert proinflammatory and vascular events. Not only the effects of smoking are due to complex actions of various substances, but, as confirmed in a recent meta-analysis, they also may be modulated by gender with females at higher risk compared with males for overall morbidity and mortality associated with smoking at low and high level of use [25]. Cigarette smoking is a risk factor for more than two dozen diseases and the single biggest cause of preventable mortality worldwide. Besides the well-known association with cardiovascular disease and several cancers, it appears to be associated with a number of inflammatory immune-related disease, and it has been strongly linked with palmoplantar pustolosis. These associations may, at least partly, explain selected comorbidities of psoriasis.

The evidence concerning the association of incident psoriasis with alcohol consumption is controversial, being partly confounded by smoking [26•]. The risk may vary depending on the type of alcoholic beverage considered. In a large-scale cohort study, nonlight beer intake was associated with an increased risk of developing psoriasis among women, whereas

Table 1 Summary of recent analytic epidemiologic studies on risk factors for incident psoriasis (for a review of earlier studies, see ref. [26•])

Country year [reference]	Study design	Study subjects	Factors analyzed	Results
Italy 2005 [17••]	Case-control	560 newly diagnosed cases and 690 controls with other skin diseases	Alcohol Smoking BMI Stressful life events	OR increased in smokers and ex-smokers: 1.7 and 1.9 respectively. Stronger association in women compared with men and in pustular psoriasis. OR 1.6 and 1.9 for overweight and obese, respectively. OR increased for increased stressful life event score
UK 2007 UKGPRD [16•]	Cohort and nested case-control	3,994 cases and 10,000 controls	Skin infection Smoking	Antecedent skin Infection OR 2.1 Smoking OR 1.4
USA 2007 Nurse Health Study II [29••]	Cohort	79,722 nurses	BMI, waist circumference, weight change	RR increases from 1.4 for BMI 21.0-22.9, to 2.69 for BMI≥35.0. Weight gain from age 18 years, higher waist circumference, hip circumference, and waist-hip ratio were all associated with a higher risk of incident psoriasis
USA 2007 Nurse Health Study II [18••]	Cohort	78,532 female nurses	Smoking	RR 1.78 for current smokers and 1.37 for past smokers. Increased risk with increased number of cigarettes smoked per day. The risk in former smokers decreases nearly to that of never smokers 20 years after cessation
UK 2008 UKGPRD [47••]	Case- control	36,702 cases and matched controls	Beta-blockers and other anti-hypertensive drugs	No association Smoking OR 1.7
Sweden 2009 [19•]	Case -control	373 cases and matched controls	Smoking BMI alcohol	BMI 9 % increased risk per unit increase
Denmark 2010 [30]	Cohort	309,152 schoolchildren	Increase in BMI	Psoriasis in adulthood associated with increase BMI at age 12 and 13 years in females only
USA Nurse Health Study II 2010 [28•]	Cohort	116,671 US female nurses	Consumption of different alcoholic beverages	RR for drinking nonlight beer (≥5 drinks/wk) 1.83. No association for light beer, wine, and liquor
Turkey 2011 [31•]	Case -control	537 cases and 511 controls younger than 18 yrs	Passive smoking, BMI, stressful life events	Passive smoking OR 2.9 Life events OR 2.9 BMI (>26) OR 2.5
USA 2012 Nurse Health Study II [45••]	Cohort	86,655 female nurses	Physical activity, vigorous exercise	RR 0.72 in the most physically active compared with the least active quintile
USA 2012 Nurse Health Study II [52•]	Cohort	86,880 female nurses	Antidepressant use Score on Mental Health Index (MHI) subscale of the Short-Form 36	RR 1.59 in women with high depressive symptomatology (MHI scores<52) or who were on anti-depressants

other alcoholic beverages, including light beer, wine, and spirits, did not increase the risk of the disease [27•]. The reasons for this specific association are unclear. A tentative explanation is that beer is one of the few nondistilled alcoholic beverages that use a starch-source for fermentation, i.e., barley. Barley contains gluten, and gluten sensitivity has been linked with psoriasis.

As documented in a meta-analysis, increased alcohol consumption is associated with prevalent psoriasis and, hence, it may represent a consequence of living with the disease [28•]. Smoking and alcohol may alter the expression of psoriasis (e.g., pattern distribution, clinical varieties) and its clinical course. Smoking has been linked with acral and pustular lesions. Alcohol has been associated with severity of psoriasis and treatment failures [26•].

Body Weight, Diet, and Physical Exercise

It is well established that increased body mass index (BMI) and increased waist circumference are risk factors for

developing psoriasis. The association has been documented, in a consistent way, both in case-control studies of incident psoriasis cases and in cohort studies [17••, 19•, 29••]. Interestingly, the association also has been found in childhood-onset psoriasis (age 0-18 years) [30, 31•, 32–34] and in psoriatic arthritis [35•, 36••]. In the largest cohort study, body mass index (BMI) information was updated every 2 years. The risk of psoriasis almost doubled in people with BMI equal or higher than 35.0 compared with people with BMI 21.0-22.9; weight gain from the age of 18 years, higher waist circumference, hip circumference, and waist-hip ratio were all associated with a higher risk of incident psoriasis [29••]. Interestingly, a multinational cross-sectional survey (not a true analytic epidemiology study) of children from nine different countries documented a similar association over the countries, of prevalent psoriasis, regardless of disease severity, with increased BMI and increased central adiposity [34]. Obesity in childhood has been associated with increased metabolic risk and cardiovascular morbidity in adulthood, hence young psoriatic patients warrant early monitoring and lifestyle modification [37]. Interestingly, significant multiplicative interaction has been recently documented in adult psoriatic patients between BMI, waist circumference, and two SNPs in the IL12B (rs3212227) and IL23R genes (rs7530511) [38].

Overweight and obesity also has been linked with a reduced response to systemic treatment in a registry of severe psoriatic patients [39], whereas, in case series, bariatric surgery and weight loss were associated with a remarkable clinical improvement of psoriasis [40]. Obesity is a metabolic and inflammatory disorder. Adipokines, e.g., chemerin, are biomarkers of obesity-related inflammation. It has been documented that patients with psoriasis have higher blood levels of adipokines, which normalize during therapy [41].

Scanty data are available concerning the role of diet in psoriasis. In an Italian case-control study, the risk of psoriasis increased with increasing BMI and was inversely related to the consumption of carrots, tomatoes, and fresh fruit and to the index of beta-carotene intake [42]. An association between gluten sensitivity, celiac disease, and psoriasis has been proposed and, recently, confirmed by a large scale cohort study of 28,958 patients suffering from celiac disease and 143,910 sex- and age-matched controls, with an hazard ratio for psoriasis of 1.78 [43••]. The association also was confirmed in children. Interestingly, in a small study of 33 psoriatic patients with antigliadin antibodies, psoriasis improved on a gluten-free diet [44]. A recent cohort study documented that vigorous physical activity was independently associated with a reduced risk of incident psoriasis [45••].

Drugs and Infections

Several drugs, e.g., lithium salts, beta-adrenergic blocking agents, antimalarials, have been reported to be responsible for the onset or exacerbation of psoriasis but evidence, with the exception of lithium salts [46••], is limited or inconclusive [47••]. A possible protective effect on psoriasis has been reported for the use of atypical antipsychotics and the oral antidiabetics thiazolidinediones [46, 48•]. Paradoxical adverse effects, defined as the onset or exacerbation of disorders that are usually improved, have been reported with tumor necrosis factor (TNF)-alpha antagonists, including new psoriasis onset. The skin lesions develop within the first few months of therapy, and patients with a wide range of underlying diseases can be affected. Palmoplantar pustulosis also is a common feature. The prevalence of this adverse effect has been estimated at 1.5-5 % of patients taking TNF-alpha antagonists [49].

An infection with beta-hemolytic streptococci often precedes the first manifestation of guttate psoriasis with an odds ratio of 7.8 estimated in an Italian case-control study [50]. Furthermore, a cohort study in the United States, involving 265,000 members of the Harvard Community Health Plan, demonstrated that chronic HIV infection is linked to a higher risk of psoriasis (relative risk 3.5). The risk increases with the progression of the disease from the asymptomatic phase to full-blown AIDS [51].

Psychosocial Factors

Psychosomatic factors are deemed to play a role in psoriasis, and stressful life events have been linked with the risk of incident psoriasis. A major problem in this area is that virtually all of the research is based on the recall of past events. People have a strong tendency to seek explanations to account for what happens to them and stress is commonly used for this. Recently, the association between depression and the risk of new-onset psoriasis was analyzed in a prospective cohort study of 86,880 American female nurses (The Nurses' Health Study II. Participants reported antidepressant use and completed the Mental Health Index (MHI), a subscale of the Short-Form 36). Depression was associated with an increased risk of incident psoriasis (relative risk 1.59; 95 % confidence interval, 1.21-2.08) [52•].

Conclusions

Genetic-environmental interaction has been proposed as a model for the causation of psoriasis. Environmental risk factors that have been proposed include smoking, alcohol consumption, diet, overweight and physical inactivity, infection, drugs, and stressful life events. Not all of them have

been adequately documented in epidemiological studies. The best documented are smoking and obesity. By imposing methodologic control and a numerate approach, epidemiology can offer a major contribution to understand the causation of psoriasis.

Conflicts of interest Dr. Naldi has received consultation fees from Novartis, Lilly, Pfitzer, Boehringer Ingelheim, and Amgen. He is an advisor for Janssen services, LLC.

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