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Psoriasis and Cardiovascular Risk: Strength in Numbers, Part II

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The Psoralen plus Ultraviolet-A (PUVA) cohort study has been a tremendous success in determining how a novel treatment (i.e., PUVA) affects the long-term risk of keratinocyte carcinoma. The ability to follow patients from the initial multicenter clinical trial for more than three decades has been a remarkable achievement in dermatoepidemiology. In this issue, Stern and Huibregtse report results from the PUVA follow-up study and conclude that only patients with exceptionally severe psoriasis have an increased overall mortality risk and that there is no significant risk of cardiovascular mortality associated with psoriasis. The results are in contrast to a large and growing body of literature that suggests patients with more severe psoriasis have a clinically significant increased risk of mortality in general and cardiovascular disease in particular. In addition, the authors found no association between severe psoriasis and obesity or between obesity and cardiovascular mortality, despite extensive literature establishing these associations. Basic principles of epidemiological study design may explain these discrepancies. Ultimately, however, randomized clinical trials will be necessary to determine whether severe psoriasis is in fact a "visible killer," as four decades ago (after many years of controversy) hypertension was recognized to be a "silent killer."

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What is known about psoriasis and cardiovascular risk?

As recently reviewed in this journal, the evolving evidence from the epidemiological literature suggests that patients with psoriasis severe enough to require systemic medications or phototherapy have an increased prevalence of major cardiovascular (CV) risk factors and a clinically significant increased risk of major CV events such as myocardial infarction, stroke, and CV death that is independent of conventional risk factors (Gelfand *et al.*, 2010). These epidemiological studies, combined with a better understanding of the pathophysiology of psoriasis, have led to the recognition that psoriasis may have the potential to affect more than skin; it is now considered a systemic inflammatory disorder (Davidovici *et al.*, 2010; Menter *et al.*, 2008).

Two recent studies have added to this previously summarized literature. First, Ahlehoff *et al.* (2010), in a nationwide Danish study of 34,371 people with mild psoriasis and 2,621 with severe psoriasis, demonstrated independent risk ratios (RRs) for CV death of 1.14 (95% confidence interval (95% CI) 1.06–1.22) and 1.57 (95% CI 1.27–1.94), respectively, with the greatest increase in young people (ages 18–50, RR 2.98, 95% CI 1.32–6.73) with severe disease. The authors also compared CV risks in patients with severe psoriasis with the risks in patients with diabetes mellitus and found comparable increases in major adverse CV events and CV deaths in these groups, demonstrating the clinical importance of the risk of CV disease attributable to psoriasis. Other recent studies have investigated the clinical significance of CV risk in patients with severe psoriasis, demonstrating that these patients have about a 6-year reduction in life expectancy and that excess risk of CV death is the largest contributor to this premature mortality (Abuabara *et al.*, 2010).

PUVA follow-up study

In contrast to all of this prior work, Stern and Huibregtse (2011) report that the risk of CV death was not increased compared with that in the US population (standardized mortality ratio (SMR) 1.02, 95% CI 0.90–1.16) and that the risk of CV death was slightly but not statistically significantly higher in patients in the highest quartile of extent of psoriasis compared with those in the lowest quartile (hazard ratio (HR) adjusted for age and sex 1.37, 95% CI 0.97–1.94, multivariate HR 1.23, 95% CI 1.23, 95% CI 0.85–1.80). Additionally, the authors found no increase in frequency of obesity in their cohort of severe psoriasis patients compared with the general US population and no statistically significant association of obesity with CV mortality, despite vast bodies of literature establishing these strong associations (Azfar and Gelfand, 2008; Davidovici *et al.*, 2010; Flegal *et al.*, 2007; Love *et al.*, 2010; Menter *et al.*, 2008; Zhang *et al.*, 2008). Basic principles of epidemiological study design

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Table 1. Relevant definitions

Bias	Any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease
Selection bias	Any systematic error that arises from methods to select participants for inclusion in a study that is differentially related to the odds of developing the outcome of interest
Information bias	Any systematic error in measuring exposure or outcome resulting in differential accuracy of information between groups
Confounding	An observed association (or lack of one) caused by a mixing of effects among the exposure, the disease, and a third factor (a confounding variable). By definition, a confounding variable is associated with the exposure and, independent of that exposure, affects the risk of developing the disease
Statistical error, type I	The effect is interpreted as significant (i.e., an association exists) when in fact the association is caused by chance. Type I error is determined by the *P* value. The risk of type I error increases with multiple comparisons
Statistical error, type II	The effect is interpreted as not significant (i.e., there is no association), when in fact the association does exist. Type II error is estimated by statistical power. The actual power of the study is determined by the range of the 95% confidence interval
Confidence interval	This represents the range within which the true magnitude of the effect in a population lies with a certain degree of confidence. With a 95% confidence interval, this means that if the study were repeated 100 times, 95% of the observations would occur within the confidence interval

From Hennekens and Buring, 1987.

may help explain the discrepancy between the mortality experience in the Psoralen plus Ultraviolet-A (PUVA) follow-up study and studies of psoriasis patients identified using population-based methods.

Principles of epidemiological study design relevant to reconciling the results

Epidemiologists attempt to design observational studies using methods that minimize bias (selection and information), confounding, and statistical error (Table 1 and Figure 1). To achieve these goals, modern approaches rely on "population-based" designs (Figure 1). Population-based studies are defined as those in which the cases (or exposed patients in cohort studies) are a representative sample of all cases (or exposed patients in cohort studies) in a well-defined population, and the controls are sampled directly from the same source population from which the cases (or exposed patients in cohort studies) were derived (Strom, 2005). Thus, an advantage of population-based studies is that the comparison group is from the same source population from which the exposed cohort was derived, a basic requirement for minimizing selection bias (Hennekens and Buring, 1987).

Selection bias. In contrast to the other studies described above, the PUVA follow-up study was not population based; subjects were derived from a clinical trial of a novel therapeutic intervention (n = 1,450) conducted at 16 leading academic dermatology centers in the United States in 1975–1976 (Melski *et al.*, 1977). Further, and critically, the study did not have an internal comparison group. Instead, the authors compared the PUVA mortality experience with that of the general US white population, calculating an SMR. Comparing a study population that was willing and able to have its health status carefully monitored by the investigators for decades with the general US white population introduces selection bias because the study subjects differ from the general white US population in important ways that could affect mortality rates. Furthermore, it has been recognized for many years that patients who participate in clinical trials tend to be healthier than patients with the disease of interest who do not participate (Britton *et al.*, 1999; Rothwell, 2005). Thus, it is probable that the study compares apples to oranges. Based on factors inherent to selection and participation, patients in the PUVA cohort are more likely to have different health-seeking behaviors, higher socioeconomic status, and access to higher-quality medical care compared with the general white US population, akin to the "healthy worker effect" in occupational cohort studies; therefore, direct comparison of these groups may be erroneous (Britton *et al.*, 1999). Moreover, even when these basic criteria are met (the best-case scenario), SMRs have been shown to underestimate mortality risk associated with exposures compared with using a more appropriate internal control group (Card *et al.*, 2006). Finally, detailed data necessary for interpreting mortality studies, such as prevalence of major risk factors for death (e.g., history of cancer, atherosclerosis, diabetes, and hyperlipidemia), are not reported.

An equally important problem with using general US rates is that they do not capture the huge variation in all-cause and CV mortality rates among states (and even within states) in the United States. For example, one of the study centers was from a state (Minnesota) that has the lowest CV mortality rate in the United States (27% lower than the national mean and 81% lower than the state with the highest CV mortality rate; Rosamond *et al.*, 2008).

As a result, one cannot determine whether the mortality experience of the PUVA cohort was attributable to the patients' being more health conscious, their having better access to medical care at academic medical centers, their having better socioeconomic status, etc., and/or the variations in mortality that exist among the states.

Information bias: measurement of outcome. In this study, mortality experience in psoriasis patients was determined on the basis of telephone interviews with patients, clinicians, or patients' relatives or extraction from death certificates and review by the authors if there was ambiguity (15% of cases). Death rates for the US population were derived from routine data sources. The different approaches used to ascertain the cause of death may introduce information bias (Table 1 and Figure 1). If this error is random, then typically bias toward the null would result. However, if the error is systematic, then the direction of bias could be difficult to determine. Importantly, the authors do not

describe any deaths related to accidents or Alzheimer's disease (the fifth and sixth most common causes of deaths in the United States; Xu, 2010). Based on routine statistics, about 31 deaths would have been expected from accidents and 19 deaths from Alzheimer's disease. The absence of these major causes of death in this study could be attributable to either the method of data extraction or the fact that this is a specialized population with mortality experience different from that of the general US population.

Information bias: measurement of exposure. Stern and Huibregtse (2011) attempt to address the fundamental limitations of their primary analysis (selection bias and the lack of an internal comparator) by examining the risk of mortality among patients with psoriasis of varying severity. Severity was assessed at one point in time and divided into quartiles based on the body surface area (BSA) involved. The lowest quartile included patients meeting the definition of moderate to severe psoriasis, and thus a comparison to an internal group of mild psoriasis patients was not conducted (Kurd and Gelfand, 2009). Psoriasis severity and exposure to the majority of covariates were based on assessment at the study outset three decades prior to study completion. Therefore, the findings represent associations between psoriasis extent *at one point in time* and mortality decades later. Changes in covariates with time were considered for smoking, PUVA, and methotrexate dose; however, these were categorized as "more than the mean exposure" that year or not, rather than either as a binary "yes/no" variable or a time-varying covariate. Given the age distribution of the study population in 1976 (5–85 years), significant changes are also likely to have occurred in psoriasis severity as well as in the measured covariates (blood pressure, body mass index) and unmeasured covariates (e.g., lipids and glucose) (Nijsten *et al.*, 2007). Additionally, several of the exposures included as confounders in this analysis (e.g., uric acid level) are potentially in the causal pathway between psoriasis and CV disease; therefore, their inclusion in multivariable analyses could erroneously mask important associations (Feig *et al.*, 2008). Given these analytic issues, the observation of excess mortality based on a single measurement of affected BSA more than 30 years earlier among a cohort of patients with severe psoriasis is remarkable. To put this finding in perspective, being in the top quartile of psoriasis severity in the PUVA cohort was associated with mortality (HR 1.55, 95% CI 1.23–1.93) to a greater extent than being in the top 15th percentile for obesity (HR 1.27, 95% CI 1.03–1.57).

Statistical error. One of the study objectives was to compare mortality experience between groups of patients with the most (n = 349) and least (n = 326) extensive psoriasis, bearing in mind that all participants had severe disease. The authors found an HR of 1.37 (95% CI 0.97–1.94) for CV mortality in the most severe group. The wide confidence interval demonstrates a lack of statistical power to detect a clinically meaningful higher CV mortality (type II error). For example, in their multivariable models the top quartile of psoriasis severity was associated with a similar degree of risk as well-established risk factors such as smoking (HR 1.35, 95% CI 1.03–1.77). Moreover, the estimate of CV mortality in the most severe group is statistically similar (based on 95% CI) to that observed in prior population-based studies assessing major CV events (Ahlehoff *et al.*, 2010; Brauchli *et al.*, 2009; Gelfand *et al.*, 2006, 2009; Kaye *et al.*, 2008; Mehta *et al.*, 2009; Xiao *et al.*, 2009).

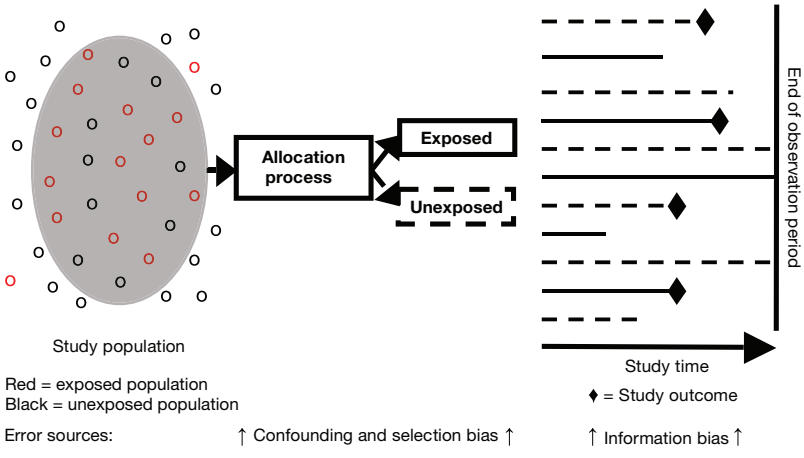

Figure 1. Unified concept of analytical epidemiology studies, highlighting the major sources of error.

What are the conclusions and future directions?

As indicated by Stern and Huibregtse (2011) and consensus statements from the editors of the *American Journal of Cardiology* and the Medical Board of the National Psoriasis Foundation, clinicians should screen patients with severe psoriasis for CV risk factors and be sure that patients with risk factors receive appropriate counseling and treatment (Friedewald *et al.*, 2008; Kimball *et al.*, 2008). The potential benefit of setting more aggressive cardioprotective treatment goals for patients with severe psoriasis, as has been recommended for patients with other inflammatory diseases having similar evidence of excess CV risk (e.g., rheumatoid arthritis), should be explored further (Peters *et al.*, 2010). To investigate these issues more fully, we have established a population-based cohort study of more than 4,000 patients with varying levels of psoriasis severity who are being followed prospectively for major CV events (Seminara *et al.*, 2010). Furthermore, based on the evolving understanding of the systemic nature of psoriasis, a critical goal is to move interventional trials in psoriasis beyond short-term assessments of changes in skin disease and quality of life, toward longer-term assessments

of the impact of treatment on the risk of developing CV, metabolic, and joint disease (i.e., psoriatic arthritis). Interestingly, the PUVA cohort found a 26% reduction in CV mortality (HR 0.74, 96% CI 0.56–0.97) in those receiving more than the mean number of PUVA treatments, suggesting that more aggressive treatment of psoriasis might improve health outcomes. Ultimately, randomized interventional trials will be necessary to determine whether severe psoriasis is in fact a "visible killer," as (after many years of controversy) randomized trials starting in the 1960s demonstrated hypertension to be a "silent killer" (Freis, 1990).

CONFLICT OF INTEREST

JMG has received grants from Amgen, Pfizer, Novartis, and Abbott and is a consultant for Amgen, Novartis, Pfizer, Abbott, Celgene, and Centocor; none of the other authors states any conflict of interest.

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