Cigarette Smoking, Body Mass Index, and Stressful Life Events as Risk Factors for Psoriasis: Results from an Italian Case–Control Study

Luigi Naldi,* Liliane Chatenoud,† Dennis Linder,* Anna Belloni Fortina,‡ Andrea Peserico,‡ Anna Rosa Virgili,§ Pier Luigi Bruni,¶ Vito Ingordo,♯ Giovanni Lo Scocco,** Carmen Solaroli,†† Donatella Schena,‡‡ Annalisa Barba,‡‡ Anna Di Landro,* Enrico Pezzarossa,§§ Fabio Arcangeli,¶¶ Claudia Gianni,♯♯ Roberto Betti,*** Paolo Carli,††† Alessandro Farris,‡‡‡ Gian Franco Barabino,§§§ and Carlo La Vecchia†¶¶¶

*Centro Studi GISED, Ospedali Riuniti di Bergamo, Bergamo, Italy; †Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; ‡Clinica Dermatologica, Università di Padova, Padus, Italy; §Clinica Dermatologica, Università di Ferrara, Ferrara, Italy; ¶Clinica Dermatologica, Università di Terni, Italy; ♯Ospedale Principale Militare Taranto, Italy; **U.O. Dermatologia, Azienda USL 4, Prato, Italy; ††Clinica Dermatologica, Università di Torino, Turin, Italy; ‡‡Clinica Dermatologica, Università di Verona, Verona, Italy; §§U.O. Dermatologia, Ospedale di Cremona, Cremona, Italy; ¶¶U.O.Dermatologia, Ospedale Bufalini, Cesena, Italy; ♯♯Dipartimento di Dermatologia, Ospedale San Raffaele, Milan, Cremona, Italy; ***Clinica Dermatologica, Ospedale San Paolo, Milan, Italy; †††Clinica Dermatologica, Università di Firenze, Florence, Italy; ‡‡‡U.O. Dermatologia, Ospedale di Savona, Savona, Italy; §§§U.O. Dermatologia, Dipartimento di Scienza della Salute, Università di Genova, Genoa, Italy; ¶¶¶Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy

We conducted a case–control study to analyse the association of psoriasis of recent onset with smoking habits, body mass index (BMI) and stressful life events. Cases (n = 560; median age 38) were patients with a first diagnosis of psoriasis and a history of skin manifestations of no longer than two years after the reported disease onset. Patients with a new diagnosis of skin diseases other than psoriasis (n = 690; median age 36) were selected as controls. The risk of psoriasis was higher in ex- and current smokers than in never-smokers, the relative risk estimates (OR) being 1.9 for ex-smokers and 1.7 for smokers. Smoking was strongly associated with pustular lesions (32 patients, OR = 5.3 for smokers). The frequency of psoriasis varied significantly in relation to a family history of psoriasis in first degree relatives, BMI (OR = 1.6 and 1.9 for over weighted, BMI 26–29, and obese, BMI ⩾ 30, respectively) and stressful life event score (compared to the lower index quartile, the OR being 2.2 for index values ⩾115). Risk estimates, when taking into consideration the combined effect of these factors with smoking habits, were consistent with a multiplicative model of risk combination with no significant statistical interaction.

Key words: body mass index/case–control study/family history/life events/psoriasis/risk factors/smoking habits
J Invest Dermatol 125:61–67, 2005

It is widely accepted that genetic–environmental interaction, i.e., multifactorial heredity, plays a role in the development of psoriasis. Although the genetic influence on psoriasis is well established, the role of environmental factors is less precisely defined. Smoking habits, alcohol consumption, diet, body mass index (BMI), stressful life events, and infections have been repeatedly considered as potentially important causative factors (Naldi, 2004). Risk estimates for these potentially modifiable factors are scanty. Such estimates as well as the analysis of the combined effect of exposure variables and the assessment of variations according to specific clinical subtypes are important pieces of evidence that may have both a theoretical value and important practical implication for the management of psoriasis and its disability prevention. We present a case–control study involving newly diagnosed cases of psoriasis and controls with newly diagnosed dermatological conditions other than psoriasis. The aim of the study was to analyze smoking habits and other commonly considered factors associated with the development of psoriasis, to explore the existence of variations in selected subgroups, and to evaluate the interaction between smoking and other documented risk factors.

Results

The distribution of cases and controls according to age, sex, marital status, family history of psoriasis in first-degree relatives, alcohol consumption, BMI, and life events index is presented in Table I. Thirty-four percent of cases reported onset before age 30. No difference was observed between cases and controls for gender, marital status, or drinking habits. The risk of psoriasis was greater in those reporting a family history of psoriasis in first-degree relatives, the adjusted OR being 5.4 (95%

Table I. Distribution of 560 cases of psoriasis and 690 controls and OR estimates according to age, sex, marital status, family history of psoriasis in first-degree relatives, alcohol consumption, BMI, and life events index (Italy, 1988–1997)

	Cases		Controls		OR[a] (95% CI)
	N[d]	Percent	N[d]	Percent	
Age (y)					
<30	188	33.6	236	34.2	1[b]
30–45	166	29.6	222	32.2	0.7 (0.5–1.1)
≥46	206	36.8	232	33.6	0.7 (0.5–1.1)
					χ^2 for trend is NS
Sex					
Males	318	56.8	345	50.0	1[b]
Females	242	43.2	345	50.0	0.9 (0.7–1.2)
Marital status					
Ever married	340	60.7	421	61.0	1[b]
Never married	220	39.3	269	39.0	1.1 (0.8–1.6)
Family history of psoriasis in first-degree relatives					
No	407	72.8	643	93.5	1[b]
Yes	152	27.2	45	6.5	5.4 (3.7–7.8)
Never drinkers	127	22.7	185	26.8	1[b]
Former drinkers	15	2.7	20	2.9	0.7 (0.3–1.6)
Drinkers, drinks per day					
<2	183	33.6	266	39.7	0.9 (0.7–1.3)
2–4	167	30.7	164	24.5	1.2 (0.9–1.8)
≥5	67	12.3	55	8.2	1.4 (0.8–2.2)
					χ^2 for trend is NS
BMI					
<26	325	59.1	483	70.5	1[b]
26–29	154	28.0	145	21.2	1.6 (1.1–2.1)
≥30	71	12.9	57	8.3	1.9 (1.2–2.8)
					χ^2 for trend 11.8 p = 0.001
Life events index[c]					
<16	39	12.9	74	25.2	1[b]
16–57	89	29.4	74	25.2	1.6 (1.0–2.5)
58–114	70	23.1	73	24.8	2.2 (1.4–3.4)
≥115	105	34.7	73	24.8	2.2 (1.4–3.4)
					χ^2 for trend 10.76 p = 0.001

[a]Multiple logistic regression estimates, including terms for sex, age, marital status, hospitalization, education level, BMI, smoking, and alcohol habits.
[b]Reference category.
[c]Information was collected from 1992 (368 cases and 360 controls).
[d]Sum of data may not equal the total because of missing values.
BMI, body mass index; OR, odds ratio; CI, confidence interval; NS, not significant.

confidence interval (CI), 3.7–7.8). The mean number of siblings was similar in cases and controls, 2.5 (standard error = 0.12) in cases and 2.2 (standard error = 0.09) in controls. The risk of psoriasis was directly related to BMI; the OR was 1.6 (95% CI, 1.1–2.1) for BMI 26–29 corresponding to overweight subjects, and 1.9 (95% CI, 1.2–

2.8) for BMI greater than 29, corresponding to obese people. An association also emerged between psoriasis and stressful life events in the year preceding the diagnosis. The life events index is presented according to the quartile distribution in the control group. The trend in risk was significant (χ^2 = 10.76, p = 0.001) but when males and

Table II. Distribution of 550 cases of psoriasis and 690 controls according to gender and smoking habits (Italy, 1988–1997)

	Males (663)		Females (587)		OR[a] (95% CI)		OR[a] (95% CI) Combined
	Cases (318) N (%)	Controls (345) N (%)	Cases (242) N (%)	Controls (345) N (%)	Males	Females	
Never smokers	81 (25.6)	120 (34.8)	122 (50.4)	220 (63.8)	1[b]	1[b]	1[b]
Former smokers	83 (26.2)	57 (16.5)	20 (8.3)	34 (9.9)	2.1 (1.3–3.5)	1.2 (0.6–2.2)	1.9 (1.3–2.7)
Smokers, cigarettes per day							
<1–10	46 (14.5)	56 (16.2)	53 (21.9)	52 (15.1)	1.3 (0.7–2.1)	2.1 (1.3–3.5)	1.6 (1.2–2.2)
11–20	72 (22.7)	77 (22.3)	42 (17.4)	36 (10.4)	1.2 (0.8–2.5)	2.3 (1.3–4.0)	1.7 (1.1–2.5)
⩾21	35 (11.0)	35 (10.1)	5 (2.1)	3 (0.9)	1.4 (0.8–2.0)	2.3 (0.4–14.2)	1.7 (1.0–3.2)
							χ^2 for trend 11.4 p<0.001
Duration of smoking habits (y)[c]							
⩽5	33 (22.1)	30 (18.1)	23 (24.7)	20 (22.2)	1.4 (0.7–2.7)	1.8 (0.8–3.9)	1.6 (0.9–2.6)
6–14	33 (22.2)	34 (20.5)	28 (30.1)	22 (24.4)	1.4 (0.7–2.5)	2.8 (1.4–5.7)	1.9 (1.2–3.0)
⩾15	83 (55.7)	102 (61.5)	42 (45.2)	48 (53.3)	1.1 (0.6–1.7)	1.5 (0.9–2.6)	1.3 (0.9–1.8)
							χ^2 for trend 5.67 p=0.017
Exposure to passive smoking[d]							
No	57 (27.5)	48 (24.6)	35 (22.2)	45 (27.6)	1[b]	1[b]	1[b]
Yes	150 (72.5)	147 (75.4)	123 (77.9)	118 (72.4)	1.0 (0.6–1.7)	1.4 (0.7–2.5)	1.6 (0.8–3.1)

[a]Multiple logistic regression estimates, including terms for age, marital status, hospitalization, education level, body mass index, smoking, and alcohol habits.
[b]Reference category.
[c]Former smokers excluded.
[d]Information was collected from 1992 (368 cases and 360 controls).
OR, odds ratio; CI, confidence interval.

females were considered separately, the trend in risk was evident for women only (data not presented).

Table II shows the distribution of cases and controls according to smoking habits for the whole sample and in gender strata. Overall, the OR for psoriasis was higher in former and current smokers. The data, however, suggested some gender differences. Male ex-smokers were at an increased risk of psoriasis; the adjusted OR for men being 2.1 (95% CI 1.3–3.5) whereas for women it was 1.2 (95% CI 0.6–2.2). For current smokers, the overall risk was 1.7 (95% CI 1.1–3.0). The risk was higher in women than men for whom the risk estimates seemed to correspond to no effect at all. When the type of cigarettes was considered categorized into four levels (very low, low, medium, and high tar concentration), no marked differences emerged; about 30% of current smokers usually smoked very low or low tar cigarettes, 63% medium tar cigarettes, and 4% high tar cigarettes, both in cases and controls (data not shown). Smoking consumption was also considered in terms of pack years, calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person had smoked. The median number of pack years was 11.8 in ex-smokers and 10.4 in current smokers (this difference was not significant). Cigars and pipe smoking accounted for only a minority of smoking habits in our population. Taking these into account did not materially change our risk estimates for smoking (data not shown).

Table III considers the combined effect of smoking and, in turn, family history of psoriasis among first-degree relatives, alcohol consumption, BMI, and life events index. The risk increased about 2-fold in smokers and drinkers as compared with non-smokers non-drinkers, and about 9-fold when smokers having a history of psoriasis in first-degree relatives were compared with non-smokers with no family history of psoriasis in first-degree relatives. The risk also increased in smokers with a higher BMI, and in smokers with a higher stressful life event index. The OR was around 3 for smokers with a BMI ⩾30 and around 5 for smokers with a life event index⩾89 (30 and 89 being the approximate tertiles of the life event index in the control group). These results are in agreement with a multiplicative model for risk combination between smoking habits and the other risk factors analyzed.

Table IV presents OR estimates for smoking habits, BMI, and life events index according to the clinical variety of psoriasis. A particularly strong association was confirmed between smoking and pustular psoriasis, OR = 5.3 (2.1–13.0).

Discussion

This study confirms that smoking, BMI, and stressful life events are independently correlated with psoriasis, and that their risks combine according to a multiplicative model without evidence for statistical interaction. Our study high-

Table III. OR estimates for psoriasis according to combined effect of smoking habits (never *vs* ever smokers) and, in turn, family history in first-degree relatives, alcohol consumption, BMI, life events index (Italy, 1988–1997)

	OR (95% CI)[a]	
	Never smokers	**Ever smokers**
Family history of psoriasis in first-degree relatives		
No	1[b]	1.7 (1.3–2.2)
Yes	5.2 (3.1–8.9)	9.2 (5.5–15.3)
Alcohol consumption		
Never drinkers	1[b]	1.8 (1.1–2.8)
Drinkers	1.2 (0.8–1.7)	1.8 (1.3–2.6)
BMI		
<26	1[b]	1.8 (1.4–2.5)
26–29	1.7 (1.1–2.7)	2.9 (1.9–4.2)
≥30	2.5 (1.3–4.5)	3.0 (1.8–5.2)
Life events index		
<30	1[b]	2.3 (1.2–4.5)
30–88	2.3 (1.2–4.4)	3.0 (1.6–5.7)
≥89	2.1 (1.1–4.1)	4.9 (2.6–9.0)

[a]Test for interaction (diff in−2 log likelihood model with and without interaction terms); sex $p = 0.416$, drinking habits, $p = 0.4$; BMI, $p = 0.8$; life events index, $p = 0.7$; family history of psoriasis $= 0.1$.
[b]Reference category.
OR, odds ratio; BMI, body mass index; CI, confidence interval.

lights a relationship between smoking and psoriasis, showing some gender difference and documenting a strong association between smoking and pustular psoriasis.

Some limitations within our study design should be considered. Our cases were patients diagnosed for the first time in their lives as suffering from psoriasis with a history of skin manifestations no longer than 2 y. Our aim was to restrict the assessment to recently developed cases. In Italy, specialist consultation is offered by the National Health Service at the request of the primary care physician and it is usual practice to refer all but the most trivial dermatology cases. We took into account the first diagnosis of psoriasis without any reference to disease severity. It is possible that the risk factors we analyzed were correlated with disease severity rather than mere disease occurrence. Unfortunately, we are unable to assess this relationship in our study. We limited the entry criteria to subjects aged 16 y or older. As a consequence, our data cannot be generalized to psoriasis with an earlier onset where other factors may play an etiologic role. The choice of dermatological controls was mainly dictated by the need to control reasons leading to specialist consultation. We are aware that this may result in overmatching (i.e., choosing controls too similar to cases for the exposure variables). Our decision to use the date of the first diagnosis by a specialist as the index date may be questionable, the major problem being the inability to separate exposures to variables prior to clinical onset from exposure to variables after clinical onset. With the exception of psychological stress, however, all the factors we analyzed were long-lasting exposures usually preceding the onset of the disease by years. The retrospective nature of our study is a more general limitation because of the potential for recall and information bias. It is reassuring to note that the prevalence of smokers in our control group was similar to the estimates obtained in a study we recently conducted on a representative sample of the Italian adult population (Naldi *et al*, 2004). The study also documented an associ-

Table IV. OR estimates for smoking habits, BMI, and stressful life events index in selected clinical varieties of psoriasis (Italy, 1988–1997)

	Guttate (N = 98)		Pustular (N = 32)		Plaque (N = 415)	
	Cases	**OR (95% CI)[c]**	**Cases**	**OR (95% CI)[c]**	**Cases**	**OR (95% CI)[c]**
Smoking habits						
Never smokers	45	1[a]	7	1[a]	143	1[a]
Smokers	46	1.4 (0.9–2.2)	21	5.3 (2.1–13.0)	181	1.6 (1.2–2.1)
Ex-smokers	7	0.7 (0.3–1.6)	4	2.3 (0.8–10.1)	90	2.2 (1.5–3.2)
BMI						
<26	65	1[a]	20	1[a]	231	1[a]
26–29	25	1.7 (1.0–3.0)	8	1.3 (0.5–3.3)	116	1.6 (1.2–2.2)
≥30	5	0.8 (0.3–2.3)	4	1.6 (0.5–5.1)	61	2.2 (1.5–3.4)
Life events index[b]						
<30	12	1[a]	5	1[a]	44	1[a]
30–88	14	1.2 (0.5–2.7)	4	0.8 (0.2–3.0)	86	1.9 (1.2–3.1)
≥89	30	2.4 (1.1–4.9)	5	1.1 (0.3–3.9)	95	2.2 (1.4–3.5)

[a]Reference category.
[b]Information was collected from 1992 (368 cases and 360 controls).
[c]Multiple logistic regression estimates, including terms for age and sex.
OR, odds ratio; BMI, body mass index; CI, confidence interval.

ation between the prevalence of psoriasis and smoking, providing further epidemiological support to our findings (data on file). Recent Italian figures indicate that greater proportions of men than women have given up smoking. The association between previous smoker status and psoriasis in men may suggest that, as compared with the controls, a greater proportion of male psoriatics gave up smoking perhaps because of very early symptoms of the disease. If selective quitting is implicated, then the risk for current smoker status among men may be underestimated by our study. The statistical power of most subgroup and interaction analyses is inadequate. As a consequence, more weight should be given to our overall results rather than to any specific result in subgroups.

Previous studies have provided some evidence for the association of psoriasis with smoking habits, BMI, and stressful life events. Interestingly, a number of diseases that are strongly linked with smoking in the general population, including among others, Crohn's disease (Lee et al, 1990), lung cancer, and tumors of the upper airways (Olsen et al, 1992; Boffetta et al, 2001) are also associated with psoriasis. Obesity has been linked with psoriasis in studies of prevalent cases (Vessey et al, 2000) and in a previous analysis of our dataset (Naldi et al, 1996). In spite of being frequently reported as a trigger, there is limited and conflicting evidence concerning the role of psychological stress in relation to the onset or exacerbation of psoriasis (Gupta et al, 1987, 1989; Picardi et al, 2001, 2003). Our study has confirmed these previously reported associations and provides evidence that stressful life events are linked to psoriasis at its first diagnosis. Several tentative biological explanations can be suggested for the associations we have documented. The following speculations are not meant to be exhaustive; they rather hint at possible connections and explanations that may be worthy of further research.

Smoke The effect of smoking is the sum of complex actions of various substances, including nicotine and carbon monoxide, and is modulated by gender, genetic background, cigarette dose, and nicotine concentration.

Psoriasis is a T cell immune-mediated disease and nicotine alters a wide range of immunological functions, including innate and adaptive immune responses (McAllister-Sistilli et al, 1998; Sopori, 2002). But contrasting results, according to the experimental model adopted, have been provided.

Nicotine can modulate the functional capacity of dendritic cells (DC) (Aicher et al, 2003; Nouri-Shirazi and Guinet, 2003). Using human and murine DC, which are professional antigen-presenting cells (APC), it has been recently documented that nicotine can concentration-dependently induce DC expression of costimulatory molecules (i.e., CD86, CD40), MHC class II, and adhesion molecules (i.e., LFA-1, CD54). Moreover, nicotine induced a significant increase in the secretion of the proinflammatory T helper 1 cytokine interleukin-12 by human DC. These effects were abrogated by the nicotinic receptor antagonists α-bungarotoxin and mecamylamine. The greater capacity of nicotine-stimulated APC to induce T cell proliferation and cytokine secretion was also documented in mixed lymphocyte reaction and antigen-specific assays. Ovalbumin-stimulated T cells from

DO10.11 mice bearing the specific transgenic T cell receptor were used (Aicher et al, 2003).

Other experiments involving chronic exposure of mice and rats have showed that cigarette smoke affects T cell responsiveness, which may account for the decreased T cell proliferative and T-dependent antibody responses in humans and animals exposed (Kalra et al, 2000). In LEW rats, a decreased response to sheep red blood cells by antibody plaque-forming cells (AFC) was also observed after intracerebroventricular administration of relatively small concentrations of nicotine (28 μg per day per kg body weight), which when given peripherally, did not affect the AFC response (Sopori et al, 1998). These results support the hypothesis that nicotine alters immune responses by directly interacting with T cells and human and/or murine DC, as well as indirectly through brain–immune interactions. In addition, nicotinic cholinergic receptors have been demonstrated on keratinocytes stimulating calcium influx and accelerating cell differentiation (Grando et al, 1996). Constant stimulation of these receptors may control keratinocyte adhesion and upward migration in the epidermis.

As we have already mentioned, psoriasis has been associated with Crohn's disease and less consistently with ulcerative colitis (Yates et al, 1982; Lee et al, 1990; Najarian and Gottlieb, 2003). A large body of evidence indicates that smoking triggers Crohn's disease and influences disease progression (Cosnes et al, 2001, 2004). As observed in psoriasis, these effects are modulated significantly by gender, with women being at a greater disadvantage than men. The possibility of a common susceptibility gene, i.e., CARD15, in Crohn's disease and psoriatic arthritis, was recently suggested (Rahman et al, 2003) but not confirmed (Giardina et al, 2004). Differing from Crohn's disease, former but not current smokers appear to be at increased risk for ulcerative colitis. It has been postulated that the withdrawal of the immunosuppressive effect of smoking triggers the disease onset in a genetically susceptible individual or simply unmasks its symptoms (Abraham et al, 2003). Such a hypothesis may be relevant to explain the association we have documented between former smoking status and psoriasis in men.

BMI BMI is a complex variable that correlates fairly well with the degree of adiposity, and is affected by both genetic and environmental factors, e.g., caloric intake (Bjorntorp, 1997; Rosenbaum et al, 1997). BMI, in turn, appears to affect several biological variables including immunity (Tanaka et al, 1993, 2001). It has been documented that circulatory levels of tumor necrosis factor (TNF)-α, soluble TNF-α receptors, and in vitro TNF-α production are significantly increased in obese subjects as compared with non-obese subjects. In obese subjects, there is a significant positive correlation between serum levels of TNF-α and waist–hip ratio, serum levels of soluble TNF-α receptor 1 and body weight, and soluble TNF-α receptor 2 and BMI. The T cell responses and previously reduced T cell subsets increase significantly following weight reduction (Tanaka et al, 2001). It has been documented that fasting may improve at least temporarily inflammatory conditions including psoriasis (Lithell et al, 1983; Kragh-Kjeldsen et al, 1991). Recently, a link has been established between obesity and a proin-

flammatory state in the so-called metabolic syndrome (Grundy *et al*, 2004).

Stress There is some evidence to suggest that psychological stress may modulate immune functions in humans and experimental animals, depending on the nature of the stressor and the immune variable under consideration (Miller *et al*, 1998). Interestingly, it has been documented that stress-induced anxiety is related to a T helper 1-like response (Maes *et al*, 1998). Based on experiments where a psychological stress was applied before immunization, it has been proposed that stress exerts an adjuvant effect on DC by promoting enhanced migration to lymph nodes and resulting in increased antigen-specific T cell responses. Such an effect appears to be modulated by release of norepinephrine by sympathetic nerve ends (Saint-Mezard *et al*, 2003).

Conclusions Our data indicate that chronic exposure to selected environmental factors, i.e., smoking, and more acute triggers, i.e., psychological stress, may influence the development of psoriasis and affect its clinical expression. The impact of the factors we have analyzed on the causation of psoriasis is far from negligible from a public health point of view. In terms of population attributable risk (Bruzzi *et al*, 1985) tobacco smoking accounted for 26% of all the psoriasis cases, family history of psoriasis in first-degree relatives accounted for 22%, and BMI accounted for 16%. When the combined effect of tobacco and BMI was considered, it accounted for 48% of all the cases in this population and 42% in people without a family history of psoriasis. Similar considerations can also apply to stressful life events.

The effect of environmental factors on the extension, distribution (e.g., acral lesions), clinical variety, and response to treatment of psoriasis should be further evaluated in prospective studies.

Subjects and Methods

The general design of this study has been previously described (Naldi *et al*, 1992, 1996, 1999). Briefly, between January 1988 and December 1997, trained interviewers identified and interviewed cases and controls using a standard questionnaire. The study was conducted in three separate periods (1988–1991, 1992–1993, 1994–1997). It was our aim to recruit about 200 cases, during each study period, with a similar number of controls. Analyses were conducted at the end of each study period and more focused hypotheses were formulated for the next study phase. These hypotheses involved amending the questionnaire and adding in new items (in particular, life events index and passive smoking were added in 1992). The study involved a total of 20 dermatologic centers from different Italian regions (14 centers from northern Italy). The results of the three phases of the study were comparable, and no significant differences between participating centers were observed. The study has been approved by the medical ethical committee of the Bergamo General Hospital. The study was conducted according to the Declaration of Helsinki Principles. Participants gave their written informed consent.

Only subjects aged 16 y or older were eligible. Entry criteria for cases were as follows: a first ever diagnosis of psoriasis made by a dermatologist and a history of skin manifestations up to 2 y after the reported disease onset. The onset was considered as the date an individual first became aware of the clinical manifestations attributable to psoriasis. The definition of onset was established by a

thorough enquiry into the timing of relevant signs and symptoms. All eligible patients who were seen consecutively during the study period were invited to participate.

A total of 560 cases (318 males, 242 females, median age 38 y) and 690 controls (345 males, 345 females, median age 36 y) were included. The psoriasis cases were classified as: psoriasis vulgaris (415, 74.1%), guttate (98, 17.5%), pustular, i.e., plaque psoriasis associated with pustular lesions and generalized pustular psoriasis (32, 5.7%), and other varieties including flexural and erythrodermic psoriasis (15, 2.7%). Controls were patients attending the same out-patient centers as the cases, with a first diagnosis of a dermatological condition other than psoriasis. Diagnoses in the control group included eczema (25%), skin cancer (16%), urticaria (14%), skin infections (13%), pityriasis rosea (10%), acne (8%), reported changes in melanocytic nevi (8%), rosacea (2%), angiomatous lesions (2%), and a variety of other skin diseases (2%). Less than 3% of cases and controls refused to be interviewed.

Information was collected on sociodemographic factors, smoking habits (daily consumption of cigarettes, cigar, and pipe), alcohol, coffee, and tea consumption, consumption of selected dietary factors, family history of psoriasis in first-degree relatives (i.e., parents and siblings), history of stressful life events, and thorough medical history. Anthropometric measures including height and weight were also obtained.

A period of abstinence of 1 y before the date of diagnosis was required for patients to be classified as ex-smokers or ex-drinkers. An Italian version of the Holmes and Rahe Social Readjustment Rating Scale was used to assess stressful life events during the year before the diagnosis. The scale included 47 items, each providing a score proportional to the associated stress, e.g., partner death (score 100), pregnancy (score 40), job troubles (score 23), small law violations (score 11, the smallest score in the scale). Total sum scores on the scale were used for the analysis.

Data analysis For each factor, we calculated the OR of psoriasis as estimates of relative risks and its corresponding 95% CI. To account simultaneously for the effects of age, sex, calendar year, and other selected covariates, unconditional multiple logistic regression with maximum likelihood fitting was used (Breslow and Day, 1980).

Attributable risks were calculated by means of the method described by Bruzzi *et al* (1985).

Supplementary Material

The following material is available from http://www.blackwellpublishing.com/products/journals/suppmat/JID/JID23681/JID23681sm.htm
Supplemental Text: Questionnaire employed to collect data.

Address correspondence to: Dr Luigi Naldi, Centro Studi GISED, Ospedali Riuniti, L.go Barozzi 1, 24100 Bergamo, Italy. Email: luigi.naldi@gised.it

References

Abraham N, Selby W, Lazarus R, Solomon M: Is smoking an indirect risk factor for the development of ulcerative colitis? An age- and sex-matched case–control study. J Gastroenterol Hepatol 18:139–146, 2003

Aicher A, Heeschen C, Mohaupt M, Cooke JP, Zeiher AM, Dimmeler S: Nicotine strongly activates dendritic cell-mediated adaptive immunity: Potential role for progression of atherosclerotic lesions. Circulation 1007:e9007–e9007, 2003

Bjorntorp P: Obesity. Lancet 350:423–426, 1997

Boffetta P, Gridley G, Lindelof B: Cancer risk in a population-based cohort hospitalized for psoriasis in Sweden. J Invest Dermatol 117:1531–1537, 2001

Breslow NE, Day NE: Statistical Methods in Cancer Research. Vol. 1. The Analysis of Case–Control Studies. No 32. Lyon, France: IARC Sci Publ., 1980

Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C: Estimating the population attributable risk for multiple factors using case–control data. Am J Epidemiol 122:904–914, 1985

Cosnes J, Beaugerie L, Carbonnel F, Genere JP: Smoking cessation and the course of Crohn's disease: An intervention study. Gastroenterology 120:1093–1099, 2001

Cosnes J, Nion-Larmurier I, Afchain P, Beaugerie L, Gendre JP: Gender differences in the response of colitis to smoking. Clin Gastroenterol Hepatol 2:41–48, 2004

Giardina E, Novelli G, Costanzo A, et al: Psoriatic arthritis and CARD15 gene polymorphisms: No evidence for association in the Italian population. J Invest Dermatol 122:1106–1107, 2004

Grando SA, Horton RM, Mauro TM, Kist DA, Lee TX, Dahl MV: Activation of keratinocyte nicotinic cholinergic receptors stimulates calcium influx and enhances cell differentation. J Invest Dermatol 107:412–418, 1996

Grundy SM, Brewer B, Cleeman JI, et al: Definition of metabolic syndrome. Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. Circulation 109:433–438, 2004

Gupta MA, Gupta AK, Haberman HF: Psoriasis and psychiatry: An update. Gen Hosp Psychiatry 9:157–166, 1987

Gupta MA, Gupta AK, Kirkby S, Schork NJ, Gorr SK, Ellis CN, Voorhees JJ: A psychocutaneous profile of psoriasis patients who are stress reactors: A study of 127 patients. Gen Hosp Psychiatry 11:166–173, 1989

Kalra R, Singh SP, Savage SM, Finch GL, Sopori ML: Effects of cigarette smoke on immune response: Chronic exposure to cigarette smoke impairs antigen-mediated signalling in T cells and depletes IP3-sensitive Ca(2+) stores. J Pharmacol Exp Ther 293:166–171, 2000

Kragh-Kjeldsen J, Haugen M, Borchgrevinck CF, et al: Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. Lancet 338:899–902, 1991

Lee FI, Bellary SV, Francis C: Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. Am J Gastroenterol 85:962–963, 1990

Lithell H, Bruce A, Gustafsson IB, et al: A fasting and vegetarian diet treatment trial on chronic inflammatory disorders. Effects on clinical condition and serum levels of neutrophil-derived granule proteins. Acta Derm Venereol (Stockh) 63:397–403, 1983

Maes M, Song C, Lin A, et al: The effects of psychological stress on humans: Increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10:313–318, 1998

McAllister-Sistilli CG, Caggiula AR, Knopf Rose CA, Miller AL, Donny EC: The effects of nicotine on the immune system. Psychoneuroendocrinology 23:175–187, 1998

Miller AH: Neuroendocrine and immune system interactions in stress and depression. Psychiatr Clin North Am 21:443–463, 1998

Najarian DJ, Gottlieb AB: Associations between psoriasis and Crohn's disease. J Am Acad Dermatol 48:805–821, 2003

Naldi L: Epidemiology of psoriasis. Curr Drug Targets, Inflammation Allergy 3:121–128, 2004

Naldi L, Colombo P, Placchesi EB, et al: Study design and preliminary results from the pilot phase of the PraKtis study: Self-reported diagnoses of selected skin diseases in a representative sample of the Italian population. Dermatology 208:38–42, 2004

Naldi L, Parazzini F, Brevi A, et al: Family history, smoking habits, alcohol consumption and risk of psoriasis. Br J Dermatol 127:212–217, 1992

Naldi L, Parazzini F, Peli L, et al: Dietary factors and the risk of psoriasis. Results of an Italian Case–Control Study. Br J Dermatol 134:101–106, 1996

Naldi L, Peli L, Parazzini F, et al: Association of early-stage psoriasis with smoking and male alcohol consumption. Evidence from an Italian Case–Control Study. Arch Dermatol 135:1479–1484, 1999

Nouri-Shirazi M, Guinet E: Evidence for the immunosuppressive role of nicotine on human dendritic cell functions. Immunology 109:329–330, 2003

Olsen JH, Møller H, Frentz G: Malignant tumors in patients with psoriasis. J Am Acad Dermatol 27:716–722, 1992

Picardi A, Abeni D: Stressful life events and skin diseases: Disentangling evidence from myth. Psychother Psychosom 70:118–136, 2001

Picardi A, Pasquini P, Cattaruzza MS, et al: Only limited support for a role of psychosomatic factors in psoriasis. Results from a case–control study. J Psychosom Res 55:189–196, 2003

Rahman P, Bartlett S, Siannis F, et al: CARD15: A pleiotropic autoimmune gene that confers susceptibility to psoriatic arthritis. Am J Hum Genet 73:677–681, 2003

Rosenbaum M, Leibel R, Hirsch J: Obesity. N Engl J Med 337:396–407, 1997

Saint-Mezard P, Chavagnac C, Bosset S, et al: Psychological stress exerts an adjuvant effect on skin dendritic cell functions in vivo. J Immunol 171:4073–4080, 2003

Sopori M: Effects of cigarette smoking on the immune system. Nat Rev Immunol 2:372–377, 2002

Sopori ML, Kozak W, Savage SM, et al: Effect of nicotine on the immune system: Possible regulation of immune responses by central and peripheral mechanisms. Psychoneuroendocrinology 23:189–204, 1998

Tanaka S, Inoue S, Isoda F, et al: Impaired immunity in obesity: Suppressed but reversible lymphocyte responsiveness. Int J Obes Relat Metab Disord 17:631–636, 1993

Tanaka S, Isoda F, Ishihara Y, Kimura M, Yamakawa T: T lymphopaenia in relation to body mass index and TNF-aplha in human obesity: Adequate weight reduction can be corrective. Clin Endocrinol (Oxford) 54:347–354, 2001

Vessey MP, Painter R, Powell J: Skin disorders in relation to oral contraception and other factors, including age, social class, smoking and body mass index. Findings in a large cohort study. Br J Dermatol 143:815–820, 2000

Yates VM, Watkinson G, Kelman A: Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. Br J Dermatol 106:323–330, 1982