

The profile of patch test reactions to common contact allergens is related to sex

JOCHEN BRASCH¹, AXEL SCHNUCH² AND WOLFGANG UTER³; FOR THE INFORMATION NETWORK OF DEPARTMENTS OF DERMATOLOGY (IVDK) IN GERMANY* AND THE GERMAN CONTACT DERMATITIS GROUP (DKG)

¹Department of Dermatology, University Clinics of Schleswig-Holstein, Campus Kiel, D-24105 Kiel, Germany,

²Center of the Information Network of Departments of Dermatology, Institute at the University of Göttingen, D-37075 Göttingen, Germany, and ³Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nürnberg, D-91054 Erlangen, Germany

Background: Women are more often patch tested than men, and the reactivity to patch test allergens is dependent on sex. However, it is unclear whether the profiles of test reactions are also sex-related.

Objective: To compare the profiles of patch test reactions of men and women.

Methods: Sex-related reaction profiles of 16 common patch test allergens were analysed based on data of 47 626 patients filed by the Information Network of Departments of Dermatology in Germany. The proportions of weak positive reactions and of questionable and irritant reactions were evaluated by calculating the positivity ratio (PR) and the reaction index (RI) separately for men and women for each allergen.

Results: Of the 16 allergens evaluated, 8 had a higher PR and a higher RI in women than in men. 4 allergens had a lower PR and another 4 had a lower RI in women than in men. For allergens with similar sensitization prevalence in men and women, female sex was associated with a higher PR and RI ($P < 0.01$).

Conclusions: There is a marginal disparity in the reactivity of men and women to patch test allergens that is probably not of clinical relevance but constitutes a scientific challenge.

Key words: contact allergy; positivity ratio; reaction index; skin reactivity. © Blackwell Munksgaard, 2007.

Accepted for publication 12 July 2007

It is a worldwide observation that the share of women in patch test patients is higher than the share of men (1–11). It is also well known that the proportions of positive patch test reactions

to many contact allergens are different for men and women (7, 9–15). Most of these differences can probably be explained by distinct sex-related patterns of allergen exposure that cause distinct

*Data of the following centers were evaluated (in alphabetical order): Aachen (C. Schröder, H. Dickel, and S. Erdmann), Augsburg (A. Ludwig), Berlin Charité (M. Worm and T. Zuberbier), Bern (D. Simon), Bochum (Ch. Szliska, H. Dickel, and M. Straube), Dermatologikum (K. Reich and V. Martin), Dortmund (C. Pirker, K. Kügler, P.J. Frosch, and R. Herbst), Erlangen (K.-P. Peters, M. Fartasch, M. Hertl, T.L. Diepgen, and V. Mahler), Freudenberg (Ch. Szliska), Gera (J. Meyer), Graz (B. Kränke and W. Aberer), Göttingen (J. Geier and Th. Fuchs), Hamburg (D. Vieluf, E. Coors, M. Kiehn, and R. Weißbecher), Hannover (T. Schaefer and Th. Werfel), Heidelberg (A. Schulze-Dirks, M. Hartmann, and U. Jappe), Heidelberg AKS (E. Weisshaar, H. Dickel, and T.L. Diepgen), Jena (A. Bauer, M. Gebhardt, M. Kaatz, S. Schliemann-Willers, and W. Wigger-Alberti), Krefeld (A. Wallerand, M. Lilie, and S. Wassilew), Lübeck (J. Grabbe and J. Kreusch), Mainz (D. Becker), Marburg (H. Löffler, I. Effendy, and M. Hertl), München LMU (B. Przybilla, P. Thomas, R. Eben, T. Oppel, and T. Schuh), München Schwabing (K. Ramrath and M. Agathos), München TU (J. Rakoski and U. Darsow), Münster (B. Hellweg and R. Brehler), Tübingen (G. Lischka, M. Röcken and T. Biedermann), Würzburg (A. Trautmann and J. Arnold).

patterns of sensitization in men and women (3, 7, 10, 12, 15) but other sex-related factors may play a role (12, 15–19). In this context, it is an interesting question whether the sex of patients may influence the quality of patch test reactions. This would result in different reaction profiles in men and women that can be quantified by the relative proportions of irritant and doubtful reactions and by different shares of weak and strong positive reactions as well.

We have addressed this question by comparing the sex-related positivity ratios (PRs) (20) and reaction indices (RIs) (21) of patch test allergens that are commonly used in standard patch test series. Our analysis is based on data of 47 626 patients of the Information Network of Dermatological Clinics (IVDK) in Germany.

Methods

The database of the IVDK was used for this retrospective analysis. As described previously (3, 22), it contains files of patients submitted to standardized patch tests by centers of dermatology. Data for this study were contributed by 25 centers in Germany, Austria, and Switzerland (see footnote on IVDK). In order to obtain as high numbers of tests as possible for a sound evaluation, only allergens of the standard patch test series were included, because these had been tested most frequently, and a time period as long as possible was chosen (10 years, 1997–2006). To optimize

data standardization for our study, out of this data pool, only those allergens were selected that had been tested in unchanged concentrations during the whole study period (Table 1), and only those tests were evaluated that had been performed with small Finn Chambers attached for 2 days to the upper back. By far most of the centers had used patch test allergens purchased from Hermal (Reinbek, Germany). The readings on D3 were used for this study. Readings had been performed and recorded according to international criteria and recommendations (23), further refined by the German Contact Dermatitis Research Group (24), of which all IVDK participants are members. Patch test reactions were classified as irritant (IR), questionable (?), weak positive (+), strong positive (++) and very strong positive reactions (+++) (23). Furthermore, age and sex of the patients were recorded in the data files as well as a history of atopic dermatitis. Only data from patients older than 17 years with no history of atopic dermatitis were included in our evaluation.

In a sex-stratified analysis, the proportions of positive reactions and the quotients of these proportions (% positive reactions in men/% positive reactions in women) were determined. Moreover, the PRs and RIs were calculated as described previously for each allergen (20, 21, 25). Briefly, the PR is obtained by dividing the number of weak positive reactions (+) found in a test population with an allergen through the number of all

Table 1. Allergens evaluated with test n, % positive reactions for men and women, the quotients of the percentages of positive reactions in men and women (% positive reactions in men/% positive reactions in women), the PRs and the RIs for men and women^a

Allergen	Numbers of patients		% Positive reactions		Quotient of % positive reactions (male/female)	PR		RI	
	Male	Female	Male	Female		Male	Female	Male	Female
Balsam of Peru 25% pet.	16 955	26 689	8.52	11.32	0.75	75.2	75.1	0.33	0.40
Benzocaine 5% pet.	14 311	22 761	1.26	1.73	0.73	63.9	65.3	0.30	0.36
Chloro-methyl-isothiazolinone 0.01 aq.	16 931	26 625	2.19	1.92	1.14	69.8	72.1	0.46	0.46
Cobalt chloride 1% pet.	16 969	26 687	3.38	6.64	0.51	75.0	66.0	–0.05	0.24
Colophony 20% pet.	16 958	26 700	4.21	5.17	0.81	56.1	62.4	0.59	0.61
Epoxy resin 1% pet.	16 955	26 755	2.16	0.92	2.35	52.9	56.5	0.46	0.22
Formaldehyde 1% aq.	16 989	26 769	1.64	1.76	0.93	74.0	78.0	0.17	0.27
Fragrance mix 8% pet.	16 954	26 671	8.68	10.58	0.82	67.1	68.4	0.46	0.49
Neomycin sulfate 20% pet.	14 620	23 227	2.50	3.21	0.78	69.6	73.4	0.46	0.43
Nickel sulfate 5% pet.	16 965	26 465	5.48	20.77	0.26	60.3	50.2	0.37	0.77
p-Phenylene-diamine 1% pet.	13 234	20 988	3.45	4.32	0.80	51.0	60.4	0.51	0.54
para-Tertiary-butylphenol-formaldehyde resin 1% pet.	16 983	26 745	0.85	1.20	0.71	69.7	65.8	0.14	0.25
Potassium dichromate 0.5% pet.	16 962	26 734	4.19	3.85	1.09	69.5	74.1	0.18	0.19
Thiuram mix 1% pet.	16 970	26 724	2.36	2.47	0.96	56.9	59.4	0.53	0.55
Oil of turpentine 10% pet.	16 973	26 745	2.22	2.37	0.94	71.8	79.5	0.35	0.30
Wool alcohols 30% pet.	16 964	26 704	3.91	4.90	0.80	79.0	80.2	0.38	0.37

Aq., aqueous; pet., petrolatum; PR, positivity ratio; RI, reaction index.

^aShaded fields (columns 7 and 8) and hatched fields (columns 9 and 10) indicate PRs and RIs, respectively, that are higher for men than for women. Bold figures (column 6) indicate a quotient of % positive reactions in men and women of <0.7 or >1.3.

positive reactions (+/++/+++) (20), and the RI is obtained by dividing the number of all positive reactions (+/++/+++) minus questionable (?) and minus irritant (IR) reactions through the sum of all non-negative reactions (?/IR/+/++/+++) (21). Summarized numbers of questionable or irritant (?/IR) and of positive reactions (+/++/+++) considering all 16 allergens found in men and women were compared with the Chi-squared test; $P < 0.05$ was considered to indicate statistically significant differences.

Results

Test results of 18 288 men and 29 338 women were evaluated; 48.6% of the men and 45.3% of the women were 18–50 years old. The numbers of patients with tests of the single allergens ranged from 13 234 to 16 989 for men and from 20 988 to 26 755 for women (Table 1).

Table 1 shows the results in detail. 16 allergens were evaluated and for each allergen the numbers of men and women tested as well as the percentages of positive reactions are listed. The numbers of tests were higher for women than for men throughout. Furthermore, 13 out of the 16 allergens had a higher percentage of positive reactions in women than in men (% positive reactions in men/% positive reactions in women < 1).

Of the 16 allergens evaluated, 8 allergens yielded both a PR and RI higher in women than in men. 4 allergens had a PR higher in men than in women (Table 1, columns 7 and 8, shaded fields), 4 had a RI higher in men than in women (Table 1, columns 9 and 10, hatched fields), but there was no allergen with both parameters, PR and RI, higher in men than in women.

For 3 allergens, the percentages of positive reactions seen in men and women were markedly different (quotient of % positive reactions in men and women < 0.7 or > 1.3 ; Table 1, column 6, bold figures): cobalt chloride, epoxy resin, and nickel sulfate. These 3 allergens also showed markedly different PRs or RIs for men and women. Cobalt chloride and nickel sulfate, both with much higher percentages of positive reactions in women than in men, had considerably lower PRs in women than in men (66.0 versus 75.0 and 50.2 versus 60.2, respectively). In contrast, epoxy resin that yielded much more positive reactions in men than in women had a markedly higher RI in men than in women (0.46 versus 0.22). For the other 5 allergens that had either a higher PR or a higher RI in men than in women, the percentages of positive reactions in men and women were only slightly different (quotient of % positive reactions in men and women between 0.7 and 1.3; Table 1,

column 6), and their values of the PRs or RIs were only marginally higher in men.

If for men and women questionable or irritant (?/IR) and positive reactions (+/++/+++) are summed up over all 13 allergens with similar percentages of positive reactions in both sexes (excluding cobalt chloride, nickel sulfate, and epoxy resin because of their markedly different percentages of positive reactions in men and women), the proportion of '?/IR' reactions among all non-negative reactions was significantly larger in men (30.8% versus 29.1%, $P = 0.002$) and, with this underlying data, the overall RI slightly, but significantly lower in men (0.385 versus 0.419). The total proportion of weak positive reactions (+) among all positive reactions (+/++/+++) (PR) in men was also significantly lower (67.9% versus 70.7%, $P < 0.0001$) than in women.

Discussion

The patch tests that were performed in men and women and that were evaluated in our study were performed by the same centers and investigators within the same period of time and by use of identical methods without considering the patients' sex. Our analysis was performed retrospectively and addresses a question that was unknown to the persons who did the patch tests and read the reactions. Therefore, bias because of patch test methods or reading standards can largely be excluded for our analysis. Because of the similar age distribution of men and women, a relevant confounding influence of the patients' age on comparisons between the 2 subgroups is also very unlikely. Furthermore, we had excluded patients with a history of atopic dermatitis from our analysis to minimize a possible confounding effect (atopic dermatitis was significantly more common in women than in men patch test patients, data not shown).

Our results show that 12 of the 16 allergens yielded a higher PR in women than in men. The PR is defined as the percentage of weak positive reactions out of all positive reaction elicited by a certain allergen (20). The mostly higher PR in women may, therefore, indicate that women are more likely to develop only weak positive reactions to common contact allergens than men, who appear to have a slightly higher tendency to show stronger positive reactions. Furthermore, in 12 of the 16 allergens a higher RI in women than in men was found. The RI relates the numbers of irritant and questionable reactions to the number of positive reactions obtained with a certain allergen (21, 25). A high RI reflects a higher proportion of positive as compared with irritant and/or questionable reactions than a low RI. Therefore,

our finding that the RI was higher in women than in men for 12 out of 16 allergens indicates that women tend to have less questionable and/or irritant reaction to common patch test allergens than men. For 8 of the 16 allergens both parameters were higher in women than in men, but the reverse constellation did not occur.

There is reason to assume that a comparison of PRs and RIs found in different populations is most convincing if the sensitization rates of the allergens in question are rather similar in the compared populations. This becomes understandable when one considers the extreme situation that PRs or RIs are compared for an allergen that is tested in a non-sensitized population and in a population with a high percentage of sensitized individuals. In the former population, only irritant and questionable reactions can occur, amongst a few (false-) weak positive ones, leading to a negative RI. In the highly sensitized population, however, mostly, or at least many, positive reactions will be found leading to a high RI. Similarly, for a certain allergen the intensity of allergic responses is presumably linked to the intensity of allergen exposure in a population which, in turn, is probably related to the percentage of sensitized individuals. In a population with a high degree of sensitization to a certain allergen a higher proportion of strong positive reactions to this allergen (resulting in a lower PR for this allergen) may, therefore, be expected than in a population with a low degree of sensitization.

Out of the 16 allergen analysed 3 showed markedly different percentages of positive reactions in men and women: cobalt chloride, nickel sulfate, and epoxy resin. Based on the considerations mentioned above it is not surprising that considerably lower PRs, and higher RIs, were found for cobalt chloride and nickel sulfate in women as compared with men, because a markedly higher percentage of positive reactions was seen with both allergens in women than in men. Accordingly, in men tests with epoxy resin resulted in a lower PR and a higher RI than in women who had a much lower percentage of positive reactions to this allergen as compared with men.

As a consequence from this likely impact of sensitization prevalence, the most meaningful comparison of reaction profiles in men and women can be expected from those allergens that elicited rather similar percentages of positive reactions in men and women. Therefore, we took a separate look at the allergens with a quotient of % positive reactions in men and women between 0.7 and 1.3. The majority (8 of 13) of these allergens had yielded higher PRs plus higher RIs in women than in men. The remaining 5 of these

13 allergens had either only a slightly higher PR or a slightly higher RI in men than in women.

In women mostly higher PRs and higher RIs are found than in men if allergens with similar percentages of positive reactions in both groups are considered. This difference is statistically significant and leads to the impression that with regard to such allergens and excluding patients with atopic dermatitis, women generally tend to have a higher proportion of weak positive reactions than men and also tend to develop less questionable and/or irritant reactions.

The combination of high PRs and high RIs is in fact a noteworthy one. It is surprising because one might speculate that a higher percentage of weak positive reactions (leading to a high PR) should be associated with more questionable or irritant reactions (thereby lowering the RI), because a clinical differentiation between questionable/irritant and weak positive reactions is often difficult and because an enhanced irritability might be associated with more weak positive reactions. Pooled data from men and women in fact indicated that in a comparison between different allergens a high PR is often related with a low RI (20, 26). Therefore, the present finding that both, the PRs and RIs, were higher in women than in men, is very interesting. It could be speculated that in women a certain number of tests which would cause questionable (erythematous) reactions in men cause 'weak positive' (erythematous and infiltrated) reactions in women. The hypothesis that in women the threshold of weak positive reactions, but not of questionable/irritant reactions and of strong positive reactions, is slightly lower than in men could explain higher RIs and PRs in women. As previous studies (with much smaller numbers of patients, however) had not shown such a difference more data are certainly needed to validate this hypothesis, but our findings are in accordance with the conclusion of a recent review that with regard to contact dermatitis sex-related differences cannot simply be reduced to a higher skin reactivity of women (15). Our results support the idea that some constitutively different responsiveness to contact allergens between men and women may exist.

If so, it can only be of a minor degree, because the absolute figures of PRs and RIs for women and men are only slightly different. Such a minimal disparity in reactivity can hardly be detected in small patch test series or by individual clinical experience and we do not believe that our findings necessitate consequences for the patch test procedures currently used in clinical routine. Nevertheless, even minor sex-related differences would be of fundamental interest for the understanding of the pathophysiology of contact allergy, and therefore,

efforts should be taken to verify our observation by other methods. If it can be confirmed it adds a new aspect to the development of contact allergic reactions that needs further characterization.

References

1. Hammershøj O. Standard patch test results in 3,225 consecutive Danish patients from 1973-1977. *Contact Dermatitis* 1980; 6: 263-268.
2. Holness D L, Nethercott J R, Adams R M et al. Concomitant positive patch test results with a standard screening tray in North America 1985-1989. *Contact Dermatitis* 1995; 32: 289-292.
3. Schnuch A. PAFS: population-adjusted frequency of sensitization. (I) Influence of sex and age. *Contact Dermatitis* 1996; 34: 377-382.
4. Liu Y Q, Zhao B, Zhuang L H, Fan W X. Patch test reactions to the Chinese Standard Screening Allergens in 1,135 patients investigated for allergic contact dermatitis. *Am J Contact Dermat* 1997; 8: 141-143.
5. Albert M R, Chang Y C, González E. Concomitant positive reactions to allergens in a patch testing standard series from 1988-1997. *Am J Contact Dermat* 1999; 10: 219-223.
6. Sertoli A, Francalanci S, Acciai M C, Gola M. Epidemiological survey of contact dermatitis in Italy (1984-1993) by GIRDCA (Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali). *Am J Contact Dermat* 1999; 10: 18-30.
7. Nielsen N H, Linneberg A, Menné T, Madsen F, Frølund L, Dirksen A, Jørgensen T. Incidence of allergic contact sensitization in Danish adults between 1990 and 1998; the Copenhagen Allergy Study, Denmark. *Br J Dermatol* 2002; 147: 487-492.
8. Wongpiyabovorn J, Puvabanditsin P. Result of standard patch test in patients suspected of having allergic contact dermatitis. *J Med Assoc Thai* 2005; 88 (Suppl. 4): 177-183.
9. Uter W, Hegewald J, Aberer W et al. The European standard series in 9 European countries, 2002/2003—first results of the European Surveillance System on Contact Allergies. *Contact Dermatitis* 2005; 53: 136-145.
10. Lindberg M, Edman B, Fischer T, Stenberg B. Time trends in Swedish patch test data from 1992 to 2000. A multi-centre study based on age- and sex-adjusted results of the Swedish standard series. *Contact Dermatitis* 2007; 56: 205-210.
11. Freireich-Astman M, David M, Trattner A. Standard patch test results in patients with contact dermatitis in Israel: age and sex differences. *Contact Dermatitis* 2007; 56: 103-107.
12. Kwangskuth C, Maibach H I. Effect of age and sex on the induction and elicitation of allergic contact dermatitis. *Contact Dermatitis* 1995; 33: 289-298.
13. Brasch J, Geier J, Schnuch A. Differenzierte Kontaktallergenlisten dienen der Qualitätsverbesserung. *Hautarzt* 1998; 49: 184-191.
14. Schnuch A, Geier J, Lessmann H, Uter W, Brasch J, Frosch P J. Kontaktallergene im aktuellen Zeitverlauf. Geschlechts- und altersspezifische Auswertungen der Daten des IVDK der Jahre 1995-2001. *Allergo J* 2004; 13: 57-96.
15. Modjtahedi B S, Modjtahedi S P, Maibach H I. The sex of the individual as a factor in allergic contact dermatitis. *Contact Dermatitis* 2004; 50: 53-59.
16. Gerretsen G, Kremer J, Nater J P, Bleumink E, de Gast G C, The T H. Immune reactivity of women on hormonal contraceptives: dinitro-chlorobenzene sensitization test and skin reactivity. *Contraception* 1978; 19: 83-89.
17. Rees J L, Friedmann P S, Matthews J N S. Sex differences in susceptibility to development of contact hypersensitivity to dinitrochlorobenzene (DNCB). *Br J Dermatol* 1989; 120: 371-374.
18. McLelland J, Lawrence C M. Premenstrual exacerbation of nickel allergy. *Br J Dermatol* 1991; 125: 83.
19. Rohold A E, Halkier-Sørensen L, Andersen K E, Thestrup-Pedersen K. Nickel patch test reactivity and the menstrual cycle. *Acta Derm Venereol* 1994; 74: 383-385.
20. Geier J, Uter W, Lessmann H, Schnuch A. The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. *Contact Dermatitis* 2003; 48: 280-282.
21. Brasch J, Henseler T. The reaction index: a parameter to assess the quality of patch test preparations. *Contact Dermatitis* 1992; 27: 203-204.
22. Uter W, Schnuch A, Geier J, Frosch P J. Epidemiology of contact dermatitis. The information network of departments of dermatology (IVDK) in Germany. *Eur J Dermatol* 1998; 8: 36-40.
23. Wahlberg J E, Lindberg M. Patch testing. In: *Contact Dermatitis*, Frosch P J, Menné T, Lepoittevin J P (eds): Berlin, Springer-Verlag, 2006: pp. 365-390.
24. Schnuch A, Aberer W, Agathos M, Brasch J, Frosch P J, Fuchs T, Richter G. Leitlinien der Deutschen Dermatologischen Gesellschaft (DDG) zur Durchführung des Epikutantests mit Kontaktallergenen. *Hautarzt* 2001; 52: 864-866.
25. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis* 1995; 33: 375-380.
26. Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis* 2007; 57: 1-10.

Address:

Professor Dr med. Jochen Brasch
 Department of Dermatology
 University Clinics of Schleswig-Holstein
 Campus Kiel
 Schittenhelmstr. 7
 D-24105 Kiel
 Germany
 Tel: +49 4315971507
 Fax: +49 4315971611
 e-mail: jbrasch@dermatology.uni-kiel.de