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Risk factors of polysensitisation to contact allergens

Running head: Polysensitisation risk factors

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Conflict of interests

The IVDK is sponsored by the cosmetic and chemical industry (associations). W.U. has accepted honoraria for presentations or travel reimbursement from cosmetic industry associations for presentations given to these. A.S. is engaged occasionally as *ad hoc* consultant for the cosmetic industry (associations), partly remunerated. J.S. and O.G. have no conflicts of interests.

- Several clinical and demographical factors were found associated with ‘polysensitisation’ in previous studies. These studies did, however, not utilise the full information available for statistical analysis.
- The present multiple hurdle regression analysis offers a more detailed estimation of the risk associated with age, gender, anatomical site and other factors. In particular, a ‘threshold risk’ to be sensitised at all, and an ‘increment factor’ for additional reactions (Polysensitisation) is separately estimated.

Abstract

Background: "Polysensitisation" (PS) is usually defined as contact sensitisation to 3 or more unrelated haptens of the baseline patch test series. Despite PS being an important clinical phenotype indicating increased susceptibility to contact allergy, statistical approaches to analyse PS have hitherto been preliminary.

Objectives: To apply an appropriate regression model for count data, namely, negative binomial hurdle regression, to a large set of clinical patch test data with the aim of estimating PS risk in more detail than previously achieved.

Methods: The detailed information provided by the hurdle model includes a separate estimation of an ‘increment factor’ quantifying the likelihood of further positive reactions, i.e. PS. Clinical data of 126878 patients patch tested by departments comprising the IVDK network (www.ivdk.org) between 1995 and 2010 were included.

Results: Regarding anatomical sites as exposure (surrogate), the axillae and the feet were found to be strong PS risk factors. Moreover, age was a strong PS risk factor, and less so, female sex. In comparison, atopic eczema and occupational dermatitis were less important risk factors. Single allergens contributed to PS to a varying extent.

Conclusion: The data presented point to some, very likely exposure-related, risk factors which need to be considered in future PS research, e.g., addressing the genetic basis for PS.

Keywords: contact allergy, hurdle regression, polysensitisation

Introduction

"Polysensitisation" (PS) has become an important concept in the clinical epidemiology of contact sensitisation. Mostly, PS has been defined as occurrence of three or more positive reactions to baseline series allergens. Regarding the definition and applications of the concept of PS, basically to identify persons who are apparently easier to sensitise than others, we refer to previous reviews on this topic ^{1, 2}.

Different statistical approaches have been used so far to examine the factors associated with PS, namely, (i) crude, bivariate analyses, (ii) logistic regression analysis and (iii) nominal and ordinal regression analysis, using an (ordered) categorical outcome. The present analysis intended to utilise the maximum information available in the original count data (individual number of positive reactions to baseline series allergens). Therefore, a conceptually suitable multiple regression method was applied to a large collection of patch test data from the Information Network of Departments of Dermatology (IVDK). The aim was to identify risk factors for PS in more detail than previously possible, e.g., regarding anatomical sites associated with PS. The improved description of the PS clinical phenotype will, in turn, be useful in future in-depth research trying to elucidate the genetic basis of (enhanced) susceptibility to allergic contact sensitisation.

Material and Methods

Clinical Data

The Information Network of Departments of Dermatology (IVDK, www.ivdk.org) is a clinical network dedicated to contact allergy surveillance in central Europe. Its methods have been

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described elsewhere ³. Briefly, patch test data are collected along with a standardised patient history and transferred to the data centre in Göttingen, Germany, twice a year in an anonymous format. Only those data complying with internal quality standards ⁴ are included in scientific analyses such as the present one. All participants of the IVDK are members of the German Contact Dermatitis Research Group (DKG) and comply with international patch test guidelines ⁵ which have been refined nationally ⁶. The German Baseline Series maintained by the DKG currently comprises 30 allergens. As PS implies sensitisation to unrelated allergens, positive reactions to related allergen preparations (in terms of the same, or a closely related substance being present in both preparations) were counted as one positive reaction. This applies to the following pairs of allergens: thiuram mix and zinc diethyldithiocarbamate, mercaptobenzothiazole and mercapto mix, fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, e.g., Lyrall TM), methyldibromoglutaronitrile and methyldibromoglutaronitrile + phenoxyethanol (Euxyl TM K 400).

The number of allergens comprising the baseline series changed slightly during the study period (see tab. 1). Four allergens in particular (paraben mix at 15% historically, and sandalwood oil, ylang-ylang oil and Jasmine abs. recently) had been tested in only about 1500 patients. While the (few) positive results are included in the calculation of PS, detailed results are not presented in tab. 1 as these would be very imprecise. Generally, patch test readings on day 3 or, if these are not available, from day 4 are analysed. Positive reactions of all grades, + to + + +, are aggregated to an outcome 'positive' as opposed to 'non-positive' reactions which comprise all other reactions (negative, doubtful, irritant). For the present analysis, patch test data from 65 centres in Germany, Austria and Switzerland, collected from 1995 to 2010 were used, amounting to a data

pool of 142470 patients. After elimination of observations with incomplete data, mostly due to missing data on anatomical site of dermatitis, 126943 patients remain in the final clinical sample.

Statistical analysis

For statistical analysis, the statistical package R (version 2.14.1⁷) was used. The requirement for a regression model was that it (i) uses the full information in the data, i.e., the original count data and (ii) offers a separate estimation of the risk of additional positive reactions and the risk of being sensitised at all. The negative binomial hurdle regression model⁸ met these requirements and was therefore used (R package ‘pscl’). This method separately estimates risk to be sensitised at all (which may depend on the selection process until patch testing⁹) and the risk of having several contact allergies, i.e., to be polysensitised. Risk factors included *a priori* in the model, based on previous, related analyses², include age, sex, atopic eczema (past or current), occupational causation of dermatitis, duration of application of the patch test (48 versus 24 hours) and anatomical site of dermatitis. Additionally, the number of individually tested allergens was controlled for, as this evidently is associated with the outcome (first, the length of different versions of baseline series differs to some extent, second, allergens are occasionally omitted on a case by case basis).

Results

Table 1 lists the single allergens comprising the German baseline series, the number of patients tested and the crude proportion of positive reactions on the left hand side. While the vastly varying prevalence of positive reactions is well known and commented on elsewhere¹⁰, the contribution of the different allergens to PS shown on the right hand side is a novel finding,

relevant for an understanding of PS. For example, nickel and thiomersal contribute relatively little, with > 40% isolated reactions due to a uniform exposure unrelated to other allergens (piercing and vaccines, resp.). In contrast, cobalt is often coupled (with nickel). A number of other, mostly fragrance or medicament, allergens show a low share of around 20 to 25 % of isolated reactions and thus a larger contribution to PS.

The distribution of the outcome variable is shown in figure 1, together with the counts predicted by the negative binomial hurdle regression model. As a first descriptive approach to examining the relationship between PS and the set of explanatory factors considered, the relative percentages of the number of positive reactions, aggregated into 3 categories for better readability and comparability with previous analyses, in the strata of explanatory factors are shown in table 2. Already this simple bivariate analysis reveals certain patterns, such as an increasing proportion of PS (“3+” reactions) with age. Specific sites may enhance the risk of sensitisation (axilla and feet due to occlusion, leg dermatitis with pre-existing inflammatory milieu) which adds to the general risk to be sensitised, thus increasing the probability of PS.

Table 3 shows the results of the mutually adjusted estimates from the negative binomial hurdle model. The exponentiated coefficients shown can be interpreted as odds ratio (OR; ‘threshold risk’) in the zero part and as relative risk (RR, ‘increment factor’) in the count part, respectively. Thereby, the former represent the risk (as OR) to be sensitised at all, the latter the risk for one more additional positive reaction. Taking, for example, sex as explanatory factor, a female patient has an expected number of positive reactions that is 12% higher than in a male patient with the same characteristics regarding age, anatomical site, etc. For instance, if a man has two positive reactions, the corresponding number is 2.24 for a woman. Evidently, these non-integer

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numbers of positive reactions cannot occur in reality; they are just theoretical estimates of the risk associated with the respective factor. Considering the ‘threshold risk’, female sex increases the odds by 71%. Compared to patients younger than 34 years, patients aged between 34 and 47 years show the greatest odds to be sensitised at all namely, a 26% increase. This ‘threshold risk’ decreases again in the two oldest age groups, whereas the ‘increment factor’ steadily increases. This divergent characteristic is discussed later.

A 2-day duration of the patch test, compared to 1 day, is neither associated with a relevant increase of the odds ratio (8%) nor with a significant ‘increment factor’. Regarding the anatomical site of dermatitis, it should be mentioned that the actual estimates, and the departure from unity of the corresponding confidence interval, depend on the choice of the reference group (in our analysis: trunk), which is arbitrary in this case of a nominally scaled variable. However, the ranking of risk estimates is interpretable and shows that leg, foot and axilla are associated with a high number of positive patch test reactions.

Discussion

Often, simple statistical models are used to evaluate medical data, since they can be applied by a broad range of researchers, and can often be easily interpreted. On the other hand, application of too simple statistics (i) may lead to erroneous conclusions, e.g., by not accounting for confounding, and (ii) may not exploit fully the information available in the data, e.g., by unnecessarily aggregating outcome or explanatory variables. In this unprecedented analyses, we have applied a multifactorial regression model which is ideally adapted to the particular distribution of our outcome variable, accounts for several explanatory factors or confounders, exploits the full information available in the data, and offers a separate estimation of an ‘increment factor’ representing PS, respectively, to examine clinical factors associated with PS.

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The current definition of PS is ‘sensitisation to three or more unrelated allergens included in the baseline series’¹¹. It should be noted that this is, to some extent, an arbitrary definition, which has become a convention. The overall yield of the baseline series⁹ (and, accordingly, the probability of diagnosing PS) will vary with the appropriateness of continually adapting this series to the currently most important contact allergens. Evidently, additional positive reactions can occur when testing additional test series, adapted to the individual patient’s history.

However, the scope of patch testing, and, with it, the probability of diagnosing (additional) contact sensitisation, would get too diverse if such individualised testing is considered. Hence, only baseline series results are included in the PS concept. Moreover, no formal evaluation of an ‘optimum cut point’ has been undertaken so far, and would probably be a futile undertaking anyway, in view of the lack of an external gold standard such as a valid genetic marker.

Furthermore, the choice of a reference group, namely, patients without positive reactions, or patients with just one specific contact sensitisation to a baseline series allergen, is not self-evident and has been handled differently in the few different studies addressing PS as outcome. Hence, there seemed no convincing reason to adhere to a certain categorical definition.

Initial results show differences between more ‘solitary’ allergens such as nickel, and more ‘co-reactive’ allergens such as Cetearyl alcohol, parabens and oil of turpentine, in line with a previous analysis¹². Furthermore, those allergens with a low proportion of no additional reactions can be considered as (very) weak allergens, which already have been shown to be associated with PS². Hence, PS is a phenomenon structured by certain groups or clusters of haptens.

When interpreting the results presented in table 3, it should be kept in mind that the novel approach of deriving two separate estimates is difficult to compare with previous results in quantitative terms. Previous analyses comparing levels of a categorical PS outcome with zero

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positive reactions as reference combine ¹³, in a way, both of our components in one model. Other analyses comparing an arbitrary level, e.g., one reaction, to another level, e.g., three or more reactions ¹⁴, only address in the limited, categorical framework, the second component of our model. Notwithstanding this interpretational difficulty related to different analytical concepts, it is interesting to compare our results with previous findings.

Sex seems to be an important risk factor for sensitisation in general but not for an exceptionally high number of positive reactions. Women apparently are found sensitised more often than men, as previous studies have already shown ¹⁵, ¹⁶. It is, however, not entirely clear whether this observation is explained by constitutional differences between the sexes ¹⁷, or by women being more intensely exposed, e.g., occupationally or to consumer products, or by both factors.

Regarding age, the chance of being sensitised and the risk of having multiple contact allergies is smallest for people younger than 34 years, our reference group. An explanation for this observation could be the shorter exposure to both consumer and working life allergens, notwithstanding some allergen exposures related particularly to young age, such as, formerly, nickel. Interestingly, the ‘threshold’ estimate decreases again for the oldest subgroup to almost the value of the youngest (reference) group. In contrast, the steady increase of the risk of multiple contact allergies with increasing age most likely reflects the effect of the cumulative exposure to a multitude of allergens during the life span, despite an apparently decreasing capacity of being newly induced (sensitised) ¹⁸.

Previous or current atopic eczema is moderately associated with PS, corresponding with findings from previous, more general analyses ¹⁹, ²⁰. Occupational dermatitis is similarly associated with PS, but more strongly than atopic eczema with having at least one contact allergy. A plausible explanation for this phenomenon is the often intense exposure to allergens during working time,

sometimes under occlusive conditions and with pre-existing skin irritation, which further facilitates sensitisation.

Patch tests are applied either for one or two days. In previous studies, more irritant and allergic reactions were seen after 48 hours allergen exposure, also in relation to the proportion of positive (allergic) reactions²¹. According to a review²² a two day application is preferable. Reassuringly, according to our multiply adjusted results, the impact of exposure time is quite minute regarding the ‘threshold risk’, and negligible (non-significant) concerning PS, respectively.

Previous studies have already shown an association between anatomical sites and sensitisation to a number of single allergens, e.g.^{23, 24}. Regarding PS, using the abovementioned categorical definition, Carlsen et al.²⁵ identified associated sites, albeit employing coarser granularity. In the ranking of risk associated with anatomical site in the categories we used, the axilla (the smallest subgroup of patients) is most strongly associated with a ‘threshold risk’. This is not surprising as the axilla is a *locus minoris resistentiae* due to semi occlusive conditions and repeated microtrauma by shaving. Thus the axillae are predisposed to sensitisation particularly to fragrance mixtures used in deodorants^{26, 27}, which may, as mixtures, additionally promote sensitisation and elicitation¹⁷. The presence of several fragrance allergens in the baseline series (the two mixes, *Myroxylon pereirae*, hydroxyisohexyl cyclohexene carboxaldehyde and oil of turpentine) may be mainly responsible for a moderately increased PS risk. Pre-existing leg ulcer or stasis dermatitis strongly predisposes to the acquisition of any contact sensitisation. The longer chronic leg ulcer is present, the more positive reactions are seen in the patient²⁸. Our results show strong associations of leg dermatitis between both the ‘threshold risk’ and PS, in line with previous findings²⁴. It must be stressed that the increase in risk we observed is not attributable to age, which is a strong confounding factor²⁹, as our analysis had been adjusted for age. Hand is, in our model, the only site showing a greater impact on PS than on ‘threshold risk’

- acknowledging that the two different risk estimates are not directly comparable numerically.

The hand is exposed to probably the broadest array of different potential allergens. In some cases, it is the only exposed site (as often in an occupational setting – included as explanatory factor), in other cases, it is co-exposed along with other sites (as, for instance, when applying body lotions, topical medications or hair cosmetics). Hence, the strong association with a vast number of allergens, ultimately leading to being a strong risk factor for PS, can be well explained. In line with our results, Carlsen et.al found an association between hand dermatitis and PS ²⁵. The feet have not yet been considered separately in previous analyses of PS. However, in view of the importance of this site presently observed, both in terms of ‘threshold risk’ and PS, its consideration seems worthwhile. Multiple allergens e.g. in shoes and socks such as dyes, glues, chromium as tanning agent, and others, may play some role as sensitisers ³⁰, in combination with aggravating factors such as occlusion, sweating and friction. Although the face is an important site, with a partly characteristic spectrum of allergens ³¹, facial contact dermatitis is not related to PS, as in the study of Carlsen et al. ²⁵. Other anatomical sites considered in our study, but not in previous analyses, are not associated with a markedly in- or decreased risk of PS.

In conclusion, our results provide an accurate description of exposure factors related to the PS clinical phenotype. This information should be taken into account in further research addressing the genetics underlying PS ¹². Moreover, longitudinal analyses should address the development of patients’ reactivity from single or ‘oligo’-sensitisation to PS, which is presumably a staggered phenomenon.

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Figure legends:

Figure 1: Number of positive reactions (bars) and predicted counts by the negative binomial hurdle regression model (dots). The percentage of positive counts is given above the bars.

Table 1: Prevalence of positive reactions to single baseline allergens and additional positive reactions (grouped) in patients patch tested in the IVDK network 1995-2010. Sodium lauryl sulphate (SLS), an ‘irritant control’, and petrolatum (vehicle control) not considered.
 “0 add”: proportion of patients without additional reactions to baseline series allergens among those with a positive reaction to the respective allergen
 “1 add”: proportion of patients with one additional reaction to a baseline series allergen among those with a positive reaction to the respective allergen
 “2+ add”: ditto, with two or more additional positive reactions
 Ordering of allergens is by decreasing proportion of 2 or more additional reactions.

	total	positive (%)	0 add	1 add	2+ add
Oil of turpentine (10%)	126077	2.20	14.2	21.5	64.3
Cetearyl alcohol (20%)	126830	0.94	16.5	21.0	62.4
Paraben mix (16%)	125813	1.33	20.6	21.2	58.2
2-Bromo-2-nitropropane-1,3-diol (Bronopol) (0.5%)	50421	1.21	21.4	22.1	56.6
Propolis (10%)	91663	2.33	20.4	24.1	55.5
Compositae mix (5%)	39645	1.35	22.5	23.1	54.4
Lanolin alcohols	126669	3.42	23.2	24.3	52.5
Colophony (20%)	126632	4.20	22.8	25.1	52.0
Mercaptobenzothiazole (2%)	85639	0.63	27.9	20.6	51.5
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (e.g. Lyrall) (5%)	75911	2.21	21.1	27.4	51.5
Mercapto mix (without MBT) (1%)	123341	0.69	27.4	22.3	50.3
Fragrance mix II (14%)	53720	4.88	23.8	26.1	50.1
N-Isopropyl-N'-phenyl-p-phenyldiamine	126812	0.73	25.9	24.3	49.8

(0.1%)

Fragrance Mix (8%)	126357	9.27	22.9	27.8	49.2
Formaldehyde (1%)	126753	1.50	24.8	26.2	48.9
Zink diethyldithiocarbamate (1%)	126830	0.53	25.5	25.8	48.7
Thiuram mix (1%)	126658	2.34	25.9	25.8	48.3
Cobalt chloride hexahydrate (1%)	126378	5.49	14.1	37.7	48.2
Potassium dichromate (0.5%)	126509	4.54	24.6	27.3	48.1
p-tert. Butylphenol formaldehyde resin (1%)	126783	0.90	29.8	22.3	47.9
<i>Myroxylon pereirae</i> (Balsam of peru) (25%)	126454	8.49	25.5	27.1	47.4
(Chloro-) Methylisothiazolinone ¹ 3:1 (0.01%)	126039	2.31	29.0	26.1	44.9
Methyldibromo glutaronitrile (0.2%)	22060	2.53	31.0	25.4	43.6
Bufexamac (5%)	91620	1.26	35.8	23.9	40.3
Epoxy resin (1%)	126632	1.33	37.5	24.6	38.0
Nickel sulfate hexahydrate (5%)	125478	14.62	46.5	27.9	25.5
Benzocaine (5%)	72854	1.48	13.6	27.6	58.9
Compositae mix (6%)	44529	2.93	18.6	22.6	58.8
Neomycin sulfate (20%)	72813	2.48	23.9	24.2	51.9
Disperse blue 124/106 mix (1%)	28318	1.20	27.1	21.4	51.5
Methyldibromo glutaronitrile + phenoxyethanol (1.0%)	53220	4.22	25.8	26.0	48.2
Methyldibromo glutaronitrile + phenoxyethanol (0.5%)	21857	2.08	25.1	26.9	48.0
p-Phenylenediamine (1%)	72365	4.20	27.5	26.1	46.4
Methyldibromo glutaronitrile (0.3%)	48823	4.85	29.6	27.8	42.6
Ammoniated mercury (1%)	72858	2.42	28.5	29.4	42.1
Thiomersal (0.05%)	50721	6.71	42.9	28.3	28.8

All allergens in petrolatum, except where otherwise

indicated: \$ water

¹ Mixture of 5-Chloro-2-methyl-isothiazol-3(2H)-one and 2-Methylisothiazol-3(2H)-one

Table 2: Proportions of (poly) sensitised patients, categorised as 0 (no sensitisation at all), 1/2 (sensitisation to one or two allergens) and 3+ (sensitisation to three or more allergens, corresponding to the conventional definition of PS) in subgroups of patients, i.e. strata of potential risk factors. Data from the IVDK network, 1995-2010.

	number	0	1/2	3+
Female sex	79321	50.9	38.1	11.0
Age:				
< 34	30611	55.8	36.8	7.4
34-47	29101	51.7	38.3	10.0
48-61	32528	55.3	34.3	10.4
≥ 62	34703	57.4	31.1	11.5
Previous or current atopic eczema	23456	52.7	36.8	10.5
Occupational dermatitis	19229	48.1	39.7	12.2
2 day duration of patch test application	92394	54.8	35.3	9.9
Site:				
Trunk	5661	58.7	33.5	7.8
Face	22254	55.1	36.5	8.4
Arm	5326	53.5	36.6	9.9
Hand	37750	52.4	36.5	11.1
Leg	15924	51.8	33.2	15.0
Foot	4907	50.5	36.1	13.4
Axilla	922	46.9	39.9	13.2
Neck	1657	52.4	38.3	9.3
Head	3820	55.8	37.7	6.5
Flexures	621	59.1	32.7	8.2
anogenital	3748	59.6	33.4	7.0
generalised	12621	61.1	30.8	8.1
Total	126943	55.2	34.9	9.9

Table 3: Estimates of OR and RR obtained from the hurdle model. Data from the IVDK network, 1995-2010.

“Zero part”: The OR denotes the odds to be sensitised at all (to at least one baseline series allergen) as a ‘threshold risk’,

“Count part”: the RR for one more additional positive reaction, respectively, associated with the risk factor as an ‘increment factor’.

	%	Zero part		Count part	
		OR	95% CI	RR	95% CI
Female sex	62.49	1.71	(1.67 ; 1.75)	1.12	(1.09 ; 1.14)
Age					
< 34	24.11	1	(reference)	1	(reference)
34-47	22.92	1.26	(1.22 ; 1.30)	1.22	(1.18 ; 1.26)
48-61	25.62	1.11	(1.08 ; 1.15)	1.38	(1.33 ; 1.43)
≥62	27.34	1.01	(0.98 ; 1.05)	1.52	(1.47 ; 1.58)
Previous or current atopic eczema	18.48	1.09	(1.06 ; 1.13)	1.11	(1.08 ; 1.15)
Occupational dermatitis	15.15	1.39	(1.35 ; 1.45)	1.10	(1.06 ; 1.14)
2 day duration of patch test application	72.78	1.08	(1.05 ; 1.11)	1.02	(0.99 ; 1.04)
Number of allergens tested	-	1.06	(1.06 ; 1.07)	1.04	(1.03 ; 1.04)
Site [§]					
Trunk	4.46	1	(reference)	1	(reference)
Face	17.53	1.03	(0.97 ; 1.10)	0.96	(0.90 ; 1.02)
Arm	4.20	1.18	(1.10 ; 1.28)	1.10	(1.01 ; 1.19)
Hand	29.74	1.14	(1.08 ; 1.21)	1.18	(1.11 ; 1.26)
Leg	12.54	1.38	(1.30 ; 1.47)	1.37	(1.28 ; 1.46)
Foot	3.87	1.45	(1.34 ; 1.57)	1.31	(1.22 ; 1.42)
Axilla	0.73	1.60	(1.39 ; 1.84)	1.26	(1.11 ; 1.44)
Neck	1.31	1.14	(1.02 ; 1.28)	0.97	(0.87 ; 1.09)
Head	3.01	1.01	(0.93 ; 1.10)	0.82	(0.75 ; 0.90)
Flexures	0.49	0.89	(0.75 ; 1.06)	1.07	(0.90 ; 1.29)
anogenital	2.95	0.99	(0.91 ; 1.08)	0.92	(0.84 ; 1.01)
generalised	9.94	0.88	(0.82 ; 0.94)	1.04	(0.97 ; 1.12)

Abbreviations: OR, Odds ratio; CI, Confidence interval; RR, risk ratio (relative risk)

[§] Not listed, but included in the regression analysis: “Other”, i.e., all remaining sites; meaningful interpretation of the OR-estimate not possible

