

Epidemiological link between wheat allergy and exposure to hydrolyzed wheat protein in facial soap

Y. Fukutomi¹, M. Taniguchi¹, H. Nakamura² & K. Akiyama¹

¹Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Sagamihara, Kanagawa; ²Department of Environmental and Preventive Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa, Ishikawa, Japan

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Correspondence

Yuma Fukutomi, MD, PhD, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan.
Tel.: +81-42-742-8311
Fax: +81-42-742-7990
E-mail: y-fukutomi@sagamihara-hosp.gr.jp

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Abstract

Background: Recent studies have highlighted the importance of extra-intestinal routes of sensitization to food-related allergens as the cause of epidemics of food allergy. Instances of Japanese women developing food allergy to wheat after exposure to hydrolyzed wheat protein (HWP) present in facial soap have been reported. However, the epidemiologic impact of these ingredients as a cause of food allergy has not been well studied.

Methods: To clarify the epidemiological relationship between food allergy to wheat and contact exposure to HWP, a case–control study of Japanese women aged 20–54 years with self-reported wheat allergy (WA) (cases, $n = 157$) and age-matched control subjects without WA (controls, $n = 449$) was performed using a large-scale Web-based research panel. Subjects answered a Web-based questionnaire regarding the use of skin and hair care products, as well as other possible risk factors.

Results: Current use of an HWP-containing facial soap (Cha no Shizuku; Yuka) was significantly associated with an increased risk of WA (adjusted odds ratio, 2.6; 95% confidence interval, 1.2–5.7; frequencies of current use in cases and controls; 11% and 6%, respectively). Use of Cha no Shizuku was more common in subjects with more recent-onset WA, implying that this soap may have contributed to the recent epidemic of WA.

Conclusions: An epidemiological relationship between WA and contact exposure to HWP has been documented. This study implicates a possible role of contact exposure to food-derived protein hydrolysates as a risk factor for the development of food allergy manifesting itself as anaphylaxis.

The burden of food allergy is an emerging public health problem worldwide (1, 2). The prevalence of adult-onset food allergy as well as childhood allergy has increased in recent decades (3). However, little is known about the cause of this increase, especially in adults. Recently, some studies have highlighted the importance of an extra-intestinal route of sensitization to food-related allergens, that is, environmental allergens, as the cause of food allergy (4–6). Birch pollen-related food

allergy (7–9) and latex–fruit allergy syndrome (10, 11) are well-studied and characterized examples of this.

Reflecting the worldwide trend toward the use of ‘natural materials’ as ingredients of skin and hair care products including facial soaps, body soaps, cosmetics, shampoo, hair treatments and hair conditioner, food-derived protein hydrolysates is becoming increasingly commonly used as moisturizers or emulsifiers. Considering the potential importance of the extra-intestinal route of sensitization, it can be hypothesized that skin and/or rhinoconjunctival exposure to these ingredients may be a cause of the development of food allergy (12–16). However, epidemiological evidence supporting this hypothesis has been limited so far.

In late 2010, a small number of cases of Japanese women with wheat-dependent exercise-induced anaphylaxis (WDEIA)

Abbreviations

AD, atopic dermatitis; AR, allergic rhinitis; BA, bronchial asthma; CIs, confidence intervals; HWP, hydrolyzed wheat protein; OR, odds ratio; WA, wheat allergy; WDEIA, wheat-dependent exercise-induced anaphylaxis.

associated with skin and/or rhinoconjunctival contact exposure to hydrolyzed wheat protein (HWP) in facial soap were reported (17, 18). After the publication of these papers, numerous similar cases have been reported from various institutions in Japan (19–23). This suggests that primary sensitization to HWP contained in skin and hair care products resulting in the development of food allergy to wheat may be relatively common in Japanese women. It is hypothesized that HWP contained in these products might be contributing to the epidemic of wheat allergy (WA) in women.

The aim of this study was to elucidate the epidemiological link between WA and exposure to HWP contained in skin and hair care products. Because WA is relatively rare in the general population, a case-control design was chosen. We used a large-scale Web-based research panel to recruit wheat-allergic patients and age-matched controls. The use of skin and hair care products containing HWP was compared between the cases and controls.

Methods

Study design

A case-control study of Japanese women aged 20–54 years was performed. Both wheat-allergic subjects (cases) and control subjects were selected from the population living in Japan, which was obtained using a large-scale Web-based

research panel. Characteristics of the studied Internet research monitor population are shown in the Supporting information. The ethics committee of Sagami Hospital approved the study protocol (No. 7 in 2010).

Web-based survey

Figure 1 shows the protocol for the Web-based survey. First, the research company sent e-mails inviting participation in the screening survey. These were sent to an age-stratified random sample of subjects in the research panel between January 14 and January 25, 2011. No further invitations were sent once 200 000 responses had been obtained. The Web-based screening questionnaire consisted of five questions regarding WA (Q1–Q5, shown in the Appendix S1). Subjects (hereafter, cases) were considered as having self-reported WA if they met the following three criteria: (i) affirmative response to Q1, 'Do you experience any allergic symptoms after eating certain foods?'; (ii) indicating 'wheat' in the response to Q2, 'Which of the foods listed below are you allergic to?'; and (iii) indicating <2 h in their response to Q3, 'How many hours after eating wheat do your allergic symptoms appear?'. Three times as many age-matched controls were also chosen from subjects who denied food allergy in Q1. Consequently, e-mail of invitations to the secondary survey was sent to 328 cases and 984 controls.

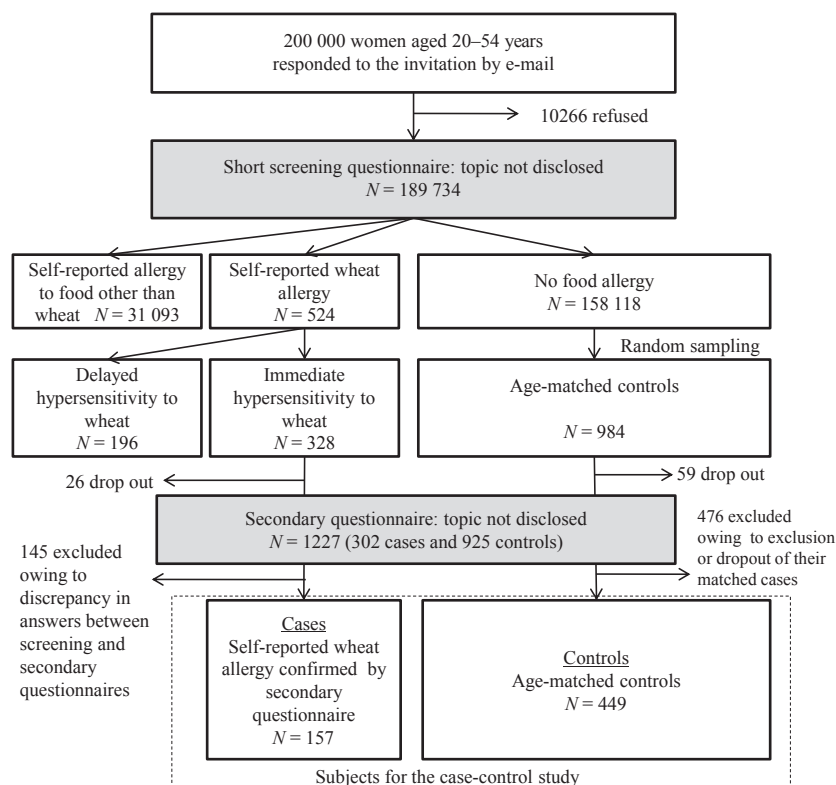


Figure 1 Protocol of Web-based survey.

The first e-mail inviting participation in the secondary survey was sent on January 28, 2011, and reminders were sent up to three times until we received answers. The secondary survey ended on February 7, 2011. The secondary questionnaire contained detailed questions regarding WA, allergic diseases other than food allergy, and use of skin and hair care products. To ensure the validity of the answers in the screening questionnaire, the secondary questionnaire included the same questions as Q1 and Q2 of the former and in addition the question 'At what age did you become allergic to wheat?', which was almost the same as Q5 of the screening questionnaire. Of the 328 cases to whom an invitation to the secondary survey was sent, 302 responded (for a response rate of 92%). We excluded 145 cases that showed discrepancies between the answers to these three questions in the screening and secondary questionnaires. Finally, data from 157 cases and 449 matched controls could be analyzed here.

Questions in the secondary questionnaire

The secondary questionnaire included questions about the use of soap, shampoo, hair treatment and conditioner, and cosmetics. All the popular brands of skin and hair care products in Japan were listed on the questionnaire, and subjects were asked to indicate which product they were 'currently using' or 'have used before' in the past 5 years. If the currently used brand was not listed, subjects were asked to provide the name of the brand they were using. If subjects gave an affirmative response for current or past use of the HWP-containing facial soap 'Cha no Shizuku' (Yuka, Fukuoka, Japan), the causal brand in most of the cases reported (17, 21), additional questions were posed on when they started to use and when they discontinued use of this brand and whether they experienced allergic symptoms after contact with the soap.

The questionnaire also included questions about possible risk factors associated with WA, namely smoking status, weight, height, allergic rhinitis (AR), atopic dermatitis (AD), and bronchial asthma (BA) comorbidities. Cases with WA were also asked whether their allergic symptoms were induced or exacerbated by exercise, whether they had been diagnosed as having WDEIA by their doctor, the frequency of WA episodes over the last 12 months, how much wheat product they consumed, and the type of symptoms induced by wheat ingestion.

Statistical analysis

The collected data were analyzed using SPSS ver. 21.0 (IBM, Tokyo, Japan). Descriptive statistics were used to characterize the cases and control subjects. Conditional logistic regression was used to compare the demographics of cases and controls and determine adjusted odds ratios (OR) and 95% confidence intervals (CIs) for the association between use of skin and hair care product and risk of WA.

The chi-square test and Fisher's exact test were used to determine whether distributions of categorical variables significantly differed from each other. Trend analysis was tested with the use of SPSS CROSSTAB command's linear-by-linear

association test. A *P*-value of ≤ 0.05 was considered statistically significant.

Results

Characteristics of cases and controls

Demographic characteristics of 157 subjects with self-reported WA and the age-matched controls are shown in Table 1. Cases were significantly more likely to have AR, BA, and AD than control subjects. In 85% of the cases, the onset of WA was in adolescence or adulthood and 52% had their WA diagnosed by a doctor.

Table 1 Demographic characteristics of cases with self-reported WA and their age-matched control subjects

	Cases (<i>n</i> = 157)	Control subjects (<i>n</i> = 449)	<i>P</i> - value
Gender (=female), <i>n</i> (%)	157 (100)	449 (100)	N.A.
Age, years, mean $\pm$ SD	35.2 $\pm$ 7.9	35.3 $\pm$ 7.8	N.A.
Allergic diseases, <i>n</i> (%)			
Allergic rhinitis	119 (76)	226 (50)	<0.001
Asthma	37 (24)	23 (5)	<0.001
Atopic dermatitis	58 (37)	56 (12)	<0.001
Smoking status, <i>n</i> (%)			
Non-smoker	117 (75)	326 (73)	0.164
Past smoker	13 (8)	62 (14)	
Current smoker	27 (17)	61 (14)	
Body mass index, kg/m ² , mean $\pm$ SD	21.6 $\pm$ 3.6	21.0 $\pm$ 3.2	0.067
Presentation of WA			
Onset age >12 years, <i>n</i> (%)	133 (85)	–	
WA diagnosed by doctor, <i>n</i> (%)	81 (52)	–	
Exacerbation of WA symptoms by exercise, <i>n</i> (%)	67 (43)	–	
WDEIA diagnosed by doctor, <i>n</i> (%)	31 (20)	–	
Frequency of episodes of WA during the last 12 months, <i>n</i> (%)			
0	28 (18)	–	
1–2	46 (29)	–	
3–5	37 (24)	–	
6–10	16 (10)	–	
11–	30 (19)	–	
How much wheat have you eaten recently?			
No wheat	13 (8)	–	
A small amount of wheat	45 (29)	–	
A usual amount of wheat	90 (57)	–	
Avoid eating only before exercise	9 (6)	–	

WA, wheat allergy; WDEIA, wheat-dependent exercise-induced anaphylaxis; N.A., not assessed.

Use of skin and hair care products as risk factors for WA

Frequencies of the use of different skin and hair care products are shown in Table 2. All brands which were currently used by more than 3% of the cases are shown in the table and were analyzed. Because comorbid allergic diseases were associated with the use of some brands of skin and hair care products (data not shown), statistical analysis of the association between the use of these products and risk of WA was performed after adjustment for AR, BA, and AD. The

Table 2 Frequency of current use of each skin and hair care product and associations with self-reported wheat allergy

Name of brand*	No. of current users (%)		Adjusted OR† (95%CI)	P-value
	Cases (n = 157)	Controls (n = 449)		
Facial soaps and body soaps				
K.B.	31 (19.7)	118 (26.3)	0.7 (0.4–1.1)	0.111
U.D.	18 (11.5)	60 (13.4)	0.8 (0.4–1.5)	0.506
Cha no Shizuku‡	17 (10.8)	26 (5.8)	2.6 (1.2–5.6)	0.014
G.C.	15 (9.6)	56 (12.5)	0.9 (0.5–1.9)	0.866
D.C.	10 (6.4)	16 (3.6)	2.2 (0.2–23.1)	0.519
U.L.	5 (3.2)	11 (2.4)	1.2 (0.4–3.7)	0.817
Shampoo				
U.L.	19 (12.1)	70 (15.6)	1.1 (0.8–1.5)	0.607
P.P.	13 (8.3)	67 (14.9)	0.7 (0.3–1.3)	0.207
S.W.‡	13 (8.3)	17 (3.8)	1.8 (0.8–4.3)	0.184
S.R.	10 (6.4)	34 (7.6)	0.8 (0.4–1.8)	0.577
C.I.‡	8 (5.1)	24 (5.3)	1.2 (0.5–3.0)	0.736
P.H.	8 (5.1)	21 (4.7)	1.3 (0.5–3.4)	0.542
S.G.	5 (3.2)	12 (2.7)	1.6 (0.5–5.1)	0.416
Hair treatment				
U.L.	17 (10.8)	66 (14.7)	0.9 (0.5–1.7)	0.755
P.P.	16 (10.2)	73 (16.3)	0.8 (0.4–1.4)	0.392
S.W.‡	12 (7.6)	17 (3.8)	1.5 (0.6–3.6)	0.416
S.R.	9 (5.7)	32 (7.1)	0.8 (0.4–1.9)	0.678
P.H.	8 (5.1)	21 (4.7)	1.5 (0.6–3.7)	0.430
C.I.‡	7 (4.5)	28 (6.2)	0.9 (0.4–2.3)	0.844
K.E.	6 (3.8)	23 (5.1)	0.5 (0.2–1.5)	0.246
K.A.	6 (3.8)	23 (5.1)	0.6 (0.2–1.6)	0.295
S.G.	5 (3.2)	11 (2.4)	1.6 (0.5–5.2)	0.404
P.V.	5 (3.2)	9 (2.0)	1.1 (0.3–4.6)	0.844
Cosmetics				
R.H.	18 (11.5)	62 (13.8)	0.8 (0.4–1.5)	0.531
D.S.‡	17 (10.8)	28 (6.2)	1.7 (0.8–3.7)	0.136
D.C.	12 (7.6)	34 (7.6)	1.2 (0.6–2.5)	0.610
F.N.	8 (5.1)	16 (3.6)	1.0 (0.4–2.6)	0.996
O.R.	7 (4.5)	24 (5.3)	0.8 (0.3–2.0)	0.581
S.E.	7 (4.5)	16 (3.6)	0.9 (0.3–2.8)	0.903
A.L.	5 (3.2)	10 (2.2)	1.3 (0.4–4.7)	0.667

OR, odds ratio.

*Names of brands other than 'Cha no Shizuku' (Yuka) are indicated by their initials.

†Adjusted for allergic rhinitis, atopic dermatitis, and asthma.

‡Some products of this brand contain hydrolyzed wheat protein.

frequency of cases currently using the HWP-containing soap, 'Cha no Shizuku', was 11%, significantly higher than in control subjects (5%, $P = 0.014$), with an adjusted OR of 2.6 (95% CIs, 1.2–5.6). As shown in Table 2, some other brands also contained HWP. However, use of no other brand showed a statistically significant association with WA. To compare the risk of WA between users of 'Cha no Shizuku' soap and users of other HWP-containing products, we performed an unconditional multivariate logistic regression analysis after adjustment for AR, BA, and AD and after limiting the subjects to those who were currently using any of the HWP-containing brands listed in Table 2. When compared with the use of other HWP-containing brands, use of 'Cha no Shizuku' was associated with an increased risk of WA with an adjusted OR of 2.3 (95%CI, 0.94–5.56) (data not shown). However, this difference did not reach statistical significance ($P = 0.07$).

Associations between the use of 'Cha no Shizuku' and WA were also evaluated using different exposure parameters. The subjects were divided into three groups according to their history of product use as follows: (i) subjects who were currently using the product (current users), (ii) those who had used it before but not currently (past users), and (iii) those who had never used it (never users). We found that only current use was associated with WA with an OR of 2.6 (1.2–5.7) (Table 3, model 1). Subjects were then divided into four groups according to the duration of use of the product. It can be seen that the duration of use ≥ 2 years was associated with an increased risk of WA with an OR of 4.2 (1.6–10.7) (Table 3, model 2). In an analysis of all subjects who had ever used the soap (current or past users), current users were more likely to have used it for ≥ 2 years ($P = 0.005$).

Of the 29 subjects who had ever used the soap (current or past users) in the allergic group, seven experienced itchiness of the face and/or eyes, sneezing, a runny nose, or

Table 3 Association between use of the facial soap 'Cha no Shizuku' containing HWP and self-reported wheat allergy

Facial soap containing HWP, 'Cha no Shizuku'	Cases (n = 157) No. (%)	Controls (n = 449) No. (%)	Adjusted OR* (95% CI)
Model 1			
History of use			
Never used	128 (82)	383 (85)	1
Ever used	12 (8)	40 (9)	1.0 (0.4–2.1)
Currently using	17 (11)	26 (6)	2.6 (1.2–5.7)
Model 2			
Duration of use			
Never used	128 (82)	383 (85)	1
<1 year	12 (8)	41 (9)	0.9 (0.4–2.1)
1 year	4 (3)	14 (3)	1.0 (0.3–3.5)
≥ 2 years	13 (8)	11 (2)	4.2 (1.6–10.7)

OR, odds ratio; 95% CI, 95% confidence interval; HWP, hydrolyzed wheat protein.

*Adjusted for allergic rhinitis, atopic dermatitis, and asthma.

swelling of the eyelids after using it (24%). This was significantly higher than in the control group (5%, 3/66) ($P = 0.008$).

Presentation of WA in relation to the use of 'Cha no Shizuku'

To further elucidate the relationship between the use of the soap and WA, we assessed associations between history of use and the presentation of WA. Figure 2 shows the frequency of current users and past users relative to the time of onset of WA. Frequencies of current users were higher in more recent-onset WA (P for trend = 0.002), suggesting that the use of the soap is associated with the recent epidemic of WA. Compared with the frequency of current users in the controls, a significantly higher frequency was observed only in cases who had developed WA within the last 4 years ($P = 0.001$). This might be explained by the fact that this facial soap started to be sold in 2004, namely 7 years before this study.

Associations between history of soap use and presentation with WA are shown in Table 4. Current use of the soap was associated with doctor-diagnosed WA. Although the overall frequency of diagnosed WA was 52%, it was as high as 76% among the current users. Additionally, eye and nose symptoms after wheat ingestion were more common among current users than never users, and about half of the current users were also diagnosed as having WDEIA by their doctor. These presentations of WA were compatible with those of

cases who were clinically diagnosed as suffering from WDEIA induced by this soap (17, 21).

Discussion

This Web-based case-control study explored epidemiological relationships between the use of the HWP-containing facial soap 'Cha no Shizuku' and risk of WA. Current use of the soap was significantly associated with increased risk of WA with an adjusted OR of 2.6. Additionally, current use of this soap was more common in cases with more recent-onset WA, implying that it may have contributed to the recent epidemic of WA. To the best of our knowledge, this is the first study that shows the epidemiological impact of contact exposure to food-derived protein in skin and hair care products on the epidemic of adult-onset food allergy.

'Cha no Shizuku' was a popular facial soap in Japan. The company (Yuka) sold more than 40 million bars to more than 4 million customers up to 2010. This product contained an acid-HWP named Glupearl 19S (Katayama Chemical, Inc, Osaka, Japan) included for its moisturizing effect and emulsification function. The soap started to be sold in 2004, and sales increased with time. A minority of allergists and dermatologists began to become aware of the potential role of HWP in this soap as an inducer of WA in 2009–2010. However, this was not recognized by the general allergist and the public until the company started a voluntary recall of the HWP-containing soap on May 25, 2011. After the voluntary recall, the allergy problem induced by this soap was publicized by the media and in the meantime has grown to be recognized as a major public health problem in Japan. Therefore, the current study was performed before the general recognition of the allergy problem. In October 2011, the Japanese Society of Allergology (JSA) determined the diagnostic criteria for the immediate WA induced by exposure to Glupearl 19S contained in this soap (21). To date, more than 2000 patients meeting these criteria have been reported to the JSA.

Among the skin and hair care products containing HWP, a statistically significant association with WA was observed only for 'Cha no Shizuku' soap. The reason for this cannot be determined from the present study. Differences in the amount of HWP in the different products may explain this, because 'Cha no Shizuku' contained the relatively high level of 0.3% of HWP. Another possibility may relate to the high volume of sales of this soap, resulting in a sufficient sample size for reliable statistical analysis. One more explanation may relate to the difference in biochemical properties between Glupearl 19S and the HWPs in other products. HWPs produced by different companies have been used in skin and hair care products in Japan. A strong sensitizing capacity of Glupearl 19S has been shown in animal models, although not in a direct comparison with other HWPs (24). Glupearl 19S contains higher molecular weight proteins, which may increase its allergenicity (25, 26). More recently, studies have shown that the deamidation of glutamine residues in gluten by acid-heat treatment also contributes to the

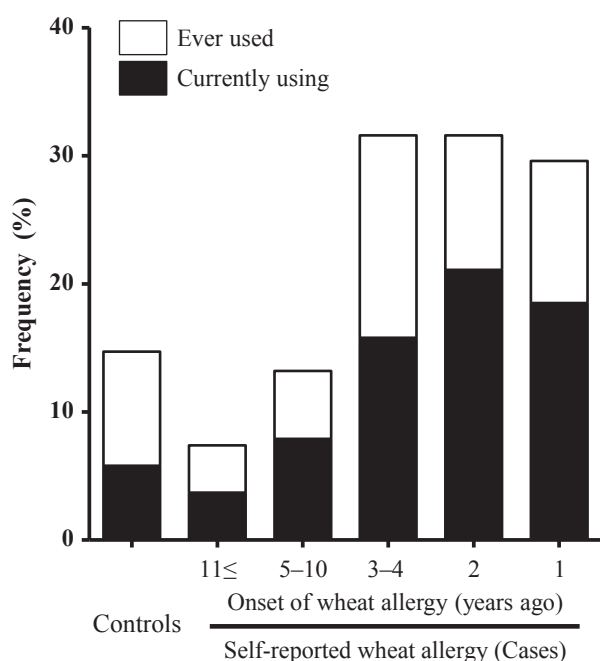


Figure 2 Frequencies of subjects who were currently using or had ever used the facial soap 'Cha no Shizuku' containing hydrolyzed wheat protein according to time of onset of wheat allergy.

Table 4 Use of the facial soap 'Cha no Shizuku' containing hydrolyzed wheat protein and the presentation of WA

	History of use			P-value
	Currently using (n = 17)	Ever used (n = 12)	Never used (n = 128)	
Onset age >12 years	17 (100)	11 (92)	102 (80)	0.079
WA diagnosed by doctor	13 (76)*	6 (50)	62 (48)	0.094
Exacerbation of WA symptoms by exercise	10 (59)	5 (42)	52 (41)	0.361
WDEIA diagnosed by doctor	8 (47)*	2 (17)	21 (16)	0.011
Frequency of episodes during the last 12 months				
0	3 (18)	2 (17)	23 (18)	0.679
1–2	3 (18)	4 (33)	39 (30)	
3–5	7 (41)	1 (8)	29 (23)	
6–10	2 (12)	2 (17)	12 (9)	
11–	2 (12)	3 (25)	25 (20)	
How much wheat have you eaten recently?				
No wheat	0 (0)	1 (8)	12 (9)	0.170
A small amount of wheat	9 (53)	2 (17)	34 (27)	
A usual amount of wheat	6 (35)	8 (67)	76 (59)	
Avoid eating only before the exercise	1 (12)*	1 (8)	6 (5)	
Self-reported symptoms of WA				
Swelling of the eyelid	9 (53)*	4 (33)	17 (13)	<0.001
Itchiness of the eyes	9 (53)*	4 (33)	25 (20)	0.008
Red swelling of the face	2 (12)	2 (17)	15 (12)	0.880
Itchiness of the face	6 (35)	2 (17)	31 (24)	0.484
Sneezing/runny nose/stuffy nose	5 (29)*	3 (25)	14 (11)	0.062
Swelling of the lips	2 (12)	2 (17)	20 (16)	0.909
Generalized itchiness	9 (53)	4 (33)	39 (30)	0.181
Generalized urticaria	8 (47)	3 (25)	32 (25)	0.157
Generalized redness	4 (24)	2 (17)	15 (12)	0.381
Discomfort or itchiness of the throat	6 (35)	3 (25)	31 (24)	0.615
Dyspnea	4 (24)	1 (8)	19 (15)	0.507
Cough	3 (18)	1 (8)	14 (11)	0.673
Wheeze/stridor	2 (12)	0 (0)	14 (11)	0.476
Abdominal pain	4 (24)*	1 (8)	8 (6)	0.052
Nausea and vomiting	3 (18)	1 (8)	9 (7)	0.328
Diarrhea	4 (24)	1 (8)	10 (8)	0.116
Blurring of vision	0 (0)	0 (0)	6 (5)	0.493
Weakness	0 (0)	0 (0)	8 (6)	0.385
Loss of consciousness	0 (0)	0 (0)	3 (2)	0.707
Palpitation	2 (12)	1 (8)	12 (9)	0.941
Headache	1 (6)	0 (0)	7 (5)	0.704
Feeling sluggish or drowsy	1 (6)	0 (0)	14 (11)	0.403

WA, wheat allergy; WDEIA, wheat-dependent exercise-induced anaphylaxis.

Data are expressed as number (%).

* $P < 0.05$ when compared with never used group.

allergenicity of acid-HWP (27–30). Additionally, the possibility remains that ingredients other than HWP in 'Cha no Shizuku' soap caused allergic contact dermatitis to disrupt the skin barrier and facilitated the penetration of higher molecular weight proteins of Glupearl 19S into an inflammatory milieu (31, 32). Indeed, the soap contained more than 10 kinds of ingredients including phenoxyethanol and 1,3-butylene glycol, which are known contact sensitizers (33, 34).

The main limitation of this study relates to the definition of WA, which was self-reported, not doctor-diagnosed. It is generally recognized that diagnosis by an allergist after provocation testing is more reliable than the definition of diseases by self-report. However, especially in the case of WDEIA, the sensitivity of the provocation test is not always very good. Using patients diagnosed by provocation test as cases may not be suitable for epidemiological studies that estimate the effect of exposure on the general population, because such patients are different from the general set of patients with WA. This study was a Web-based survey; such surveys have the advantage that both cases and controls can be recruited from the same cohort of the general population, and patients with rare diseases are identifiable in large-scale cohorts.

In conclusion, this Web-based case-control study documents an epidemiological relationship between WA and contact exposure to HWP in Japanese women. These findings imply a possible role of contact exposure to food-derived protein hydrolysates in skin and hair care products in the epidemic of adult-onset food allergy. We urge that more attention should be paid to the possible role of food-derived protein in skin and hair care products in the induction of food allergy.

Author contributions

YF designed the study and wrote the manuscript. MT, HN, and KA contributed to the critical revision of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

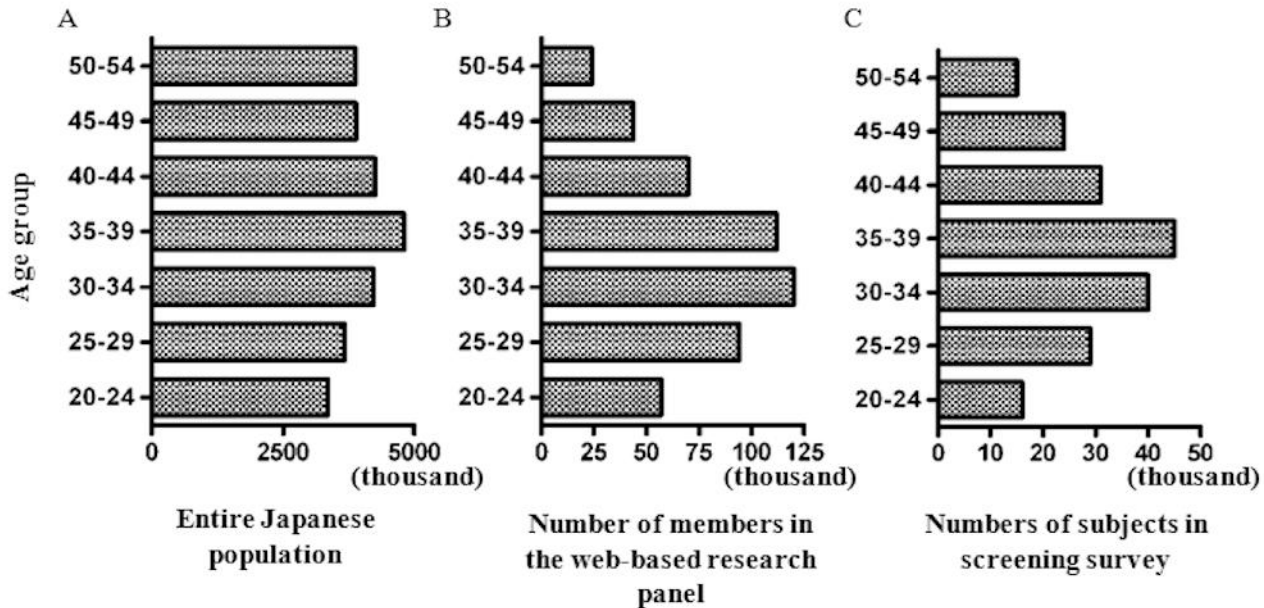
Figure S1. Distribution of the population of 20–54 year-old women in Japan according to the national population census (A), the number of women aged 20–54 years who were registered to MACROMILL research panel in 2011 (B), and number of studied subjects in the screening survey (C).

Appendix S1. Screening questionnaire.

Data S1. Characteristics of the studied internet research monitor population.

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Supporting information

<Appendix>

Screening Questionnaire

Q1 Do you experience any allergic symptoms after eating certain foods?

Note 1: If you have previously had a food allergy but do not have it any more, answer “No.”

Note 2: If you do not necessarily experience allergic symptoms each time you eat a certain food but experience them depending on your condition, answer “Yes.”

Note 3: If you experience allergic symptoms only when you exercise after having eaten a certain food, also answer “Yes.”

Yes / No

(Condition: Answer question Q2 only if you answered “Yes” to question Q1.)

Q2 Which of the foods listed below are you allergic to? Mark all choices that apply.

(If you do not necessarily experience allergic symptoms each time you eat a certain food but experience them depending on your condition, mark this food.)

Eggs, Milk/dairy products, Wheat, Shrimp, Crab, Peanuts, Nuts, Buckwheat, Fruit, Soybeans, Vegetables, Fish, Shellfish, Squid, Octopus, Beef, Pork, Chicken, Food additives, Other ()

(Condition: Answer questions Q3, Q4, and Q5 only if you answered “Wheat” to question Q2.)

Q3 How many hours after eating wheat do your allergic symptoms appear? Mark the answer that applies best.

Within 2 hours of eating wheat / More than 2 hours after eating wheat

Q4 Have you ever been diagnosed as having “a wheat allergy” by a doctor?

Yes / No

Q5 How many years ago did you first experience allergic symptoms after eating wheat?

Mark the answer that applies best.

Within 1 year / 1–2 years ago / 2–3 years ago / 3–4 years ago / 4–5 years ago / 5–10 years ago /

More than 10 years ago

Supporting information

Characteristics of the studied internet research monitor population

MACROMILL, INC (Tokyo, Japan) is a Japanese research company that maintains a web-based research panel, one of the largest in Japan. Members of research panels are voluntary registrants who have agreed to answer various web-based surveys for a small fee (Membership point). The number of registered members at the time of this study was approximately one million, representing 0.8% of the Japanese population. The number of women aged 20-54 yrs. was approximately 520,000, representing 1.9% of Japanese women in this age group.

As shown in Figure S1, the age-distribution of the MACROMILL^{o,R} research panel (Figure S1 B) was different from that of the entire Japanese population (Figure S1 A). To increase the representativeness of the study, the age-distribution of the studied subjects was standardized to that of the entire population as far as possible. However, we could not standardize it completely because of the limited size of the research panel of subjects aged 20-24 and 50-54 yrs. Consequently, the proportion of studied subjects aged 20-24 and 50-54 yrs. in the screening survey were smaller than that of the entire Japanese population, as shown in Figure S1 C.

Supporting information

Figure legend

Figure S1. Distribution of the population of 20-54 year-old women in Japan according to the national population census (A), the number of women aged 20-54 yrs. who were registered to MACROMILL research panel in 2011 (B), and number of studied subjects in the screening survey (C)