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Elimination diet and the development of multiple tree-nut allergies

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ABSTRACT

Background

Despite its high prevalence, relatively little is known about the characteristics of patients with multiple tree-nuts allergies.

Methods

Patients (n=60, aged 4 – 15 years), recruited for a multiple food (tree-nuts, peanut, milk, egg, soy, sesame and wheat) oral immunotherapy (OIT) study, filled a questionnaire on their initial allergy evaluation. Medical records were reviewed. At OIT enrollment (median interval, 7.5 years), patients underwent oral food challenges (OFC) to foods still eliminated.

Results

There was significantly less evidence for eliminating tree-nuts compared to other foods, as reflected by lower rate of acute reaction to the offending food, either as the trigger for initial allergy evaluation (5.9% for tree-nuts vs. 20%-40% for other foods, respectively $p<0.001$), or later in life (14.5% vs. 38%-75%, respectively $p=0.001$), and a higher rate of negative SPT/sIgE at initial diagnosis (25% vs. <10%, $p<0.001$). SPT/sIgE increased significantly from past initial levels to present for tree-nuts ($p<0.001$) and peanut ($p=0.001$) but not for other foods, and most OFCs performed at present were positive.

Conclusions

Tree-nuts are often eliminated from the diet of multiple food-allergic patients, despite low probability for allergy. Sensitization and allergy to most tree-nuts exist years later suggesting it developed during the period of elimination.

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INTRODUCTION

It is estimated that 2.4% of the population and 30.4% of patients with food allergy suffer from multiple food allergies (1, 2). A higher frequency of multiple food allergies has been described in certain populations. Patients with peanut allergy were reported to have high sensitization rates, reaching up to 86%, to tree-nuts and to frequently have concomitant clinical allergy (3, 4). Also, patients who are allergic to a single tree-nut are frequently sensitized to additional tree-nuts and sensitization to other tree-nuts among tree-nut allergic children has already been detected at age <1 year in 25% of patients (5). Patients with atopic dermatitis, especially those with moderate-severe disease, comprise another group with a high frequency (up to 30%) of multiple food allergies, and they are frequently sensitized to multiple foods (6, 7).

Self-reported food allergy is subjective and inaccurate (8), and testing for food-specific IgE by skin test or in vitro laboratory testing is only moderately specific (1, 9). Therefore, a double-blind placebo-controlled food challenge (DBPCFC) or alternatively an open oral food challenge (OFC), is therefore recommended before a diagnosis of food allergy can be made and elimination diet initiated (10). However, OFCs are time-consuming, often associated with adverse events, and are not without risks (11, 12). Therefore, OFCs might be difficult to perform in a child with multiple sensitizations. As a result, detecting multiple sensitizations in a child, might lead to an extensive elimination diet.

Prescribing an extensive elimination diet for a child without rigorously confirming its need may significantly impair the child's nutritional needs (13) as well

as quality of life (14). Moreover, recent data suggest that eliminating peanuts from the diet may in itself increase the risk of developing IgE-mediated peanut allergy (15-16).

Given the increased prevalence of multiple food allergies and the risks of extensive elimination diet, it is important to understand “real life” approaches by allergists and pediatricians to the diagnosis of patients with multiple food allergies and to prescribing elimination diet. The goal of the present study was to examine the history of a selected group of patients, currently diagnosed with multiple food allergies and enrolled in a multiple food oral immunotherapy (OIT) research, including reasons for elimination of individual foods, evidence and level of previous sensitization, and documented reactions.

MATERIALS AND METHODS

Patients

This study is the baseline description of 60 patients, >4 years old, enrolled to multiple OIT treatment research program. For inclusion, patients had to have Skin prick test (SPT) ≥ 6 mm wheal diameter or sIgE > 4 kU_A/L (ImmunoCAP) and to react to ≤ 500 mg cumulative food protein on a DBPCFC, to at least 2 allergens (of the following: peanut, milk, egg, soy, sesame, wheat, cashew, walnut, hazelnut, almond). SPT and sIgE were performed to pistachio and pecan as well, and food challenges were done for patients fulfilling inclusion criteria. Information on demographics and past medical history was obtained from all patients, including age and reason for elimination of each food from the diet, occurrence and nature of previous adverse reactions, and oral food challenges performed. Patients' medical records were reviewed and skin prick tests (SPTs) and sIgE levels from the time food elimination was initiated, were collected. The study was approved by the Stanford IRB committee.

Skin prick tests

Past SPT's, performed when elimination diet was initiated, were done by local allergists and documents were reviewed by an allergy specialist (Dr. Elizur). Current SPT's were performed by trained staff with the following extracts: peanut (1:20 W/V), almond (1:20 W/V), pecan (1:20 W/V), milk (1:20 W/V), sesame seed (1:20 W/V), egg white (1:20 W/V), cashew (1:20 W/V), walnut (1:20 W/V), whole wheat (1:20 W/V), hazelnut (1:20 W/V), soybean (1:40 W/V) (Greer Laboratories, Lenoir, NC) and pistachio (1:10 W/V, ALKPort Washington, NY). Histamine (10 mg/ml, Hollister-Stier,

Spokane WA) was used as a positive control and physiological saline as a negative control.

Food Challenges

All food challenges performed during OIT enrollment were performed at SNP Center for Allergy and Asthma Research at Stanford University under medical supervision and patients were observed for at least two hours after the last dose. Seven doses of food allergens were given every 15-30 minutes in increasing amounts (5 mg, 20 mg, 50 mg, 100 mg, 100 mg, 100 mg, and 125 mg) up to a cumulative total of 500 mg of protein. Reactions during each oral food challenges were scored based on modified Bock's criteria (17) and treated according to guidelines (10).

Statistical analysis

Statistical analyses were performed using SPSS software (version 20; SPSS, Inc, Chicago, Ill). The Mann-Whitney test was used for non-normally distributed continuous variables. Fisher's exact test was used to analyze differences in categorical variables. Kruskal Wallis test was performed to analyze differences between multiple continuous variables. All analyses were 2-tailed and a P-value of less than 0.05 was considered significant. Bonferroni correction was applied when multiple comparisons were made. For the purpose of statistical analysis, SPT wheal size (mm) and sIgE levels (kIU/L) from the time patients were diagnosed were categorized as follows: grade 0 (SPT=0 and sIgE<0.35), grade 1 ($1 \leq \text{SPT} \leq 4$ or $0.35 < \text{sIgE} \leq 3.5$) grade 2 ($5 \leq \text{SPT} \leq 8$ or $3.5 < \text{sIgE} \leq 17.5$) and grade 3 ($\text{SPT} > 8$, $\text{sIgE} > 17.5$). Grading was done based on levels

that were previously described as significant (18-20) and the highest grade (SPT vs. sIgE) was used for the analysis.

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RESULTS

Patient age ranged between 4 to 15 years with a median of 8 and most were White or Asian (**Table 1**). Most patients had other allergic comorbidities, in addition to food allergy. Atopic dermatitis was the most frequent (76.7%) comorbidity and in the case of 31.7% of the patients it was felt to be triggered/exacerbated by the allergenic food. An acute reaction to a single food item was the most common trigger for allergy evaluation, at time of initial diagnosis, accounting for 70% of the cases. Milk (n=11), peanut (n=9) and a single tree-nut (n=15) were the most frequent triggers. In 6 patients (10%) the reaction occurred to a mixture of foods and an individual trigger could not be identified. Allergy tests were performed solely due to eczema in 9 patients (13%) and in additional 7% due to other reasons (family history of food allergy, n=2; rectal bleeding, n=1; and occasional vomiting not related to food, n=1). Following their initial allergy evaluation and initial SPT/sIgE tests, and although a reaction to a single food was often documented, patients were instructed to eliminate a median of 8 foods (range, 2 – 11) from their diet. Cashew, hazelnut, pecan, pistachio, and walnut were each eliminated by 58 patients, peanut by 50 patients, almond by 47 patients, milk by 29 patients, egg by 30 patients, soy by 9 patients, sesame by 23 patients, and wheat by 5 patients. Of the 220 foods that were eliminated without evidence of a previous reaction, all cases of milk, soy and egg elimination began before age 1.5 years. Most peanuts and tree-nuts were eliminated before age 4 years, when, according to previous guidelines, introduction, especially to atopic children, was not yet recommended. Only 5 patients had allergy evaluation for specific foods beyond the age of 4 years. In 2 patients, eliminated foods were not introduced in the home because of allergic siblings, in one

case a deliberate elimination of peanuts and all tree-nuts was done by the mother, without allergy evaluation, following a reaction to cashew in infancy, and 2 patients eliminated sesame without allergy testing due to peanut and tree-nut allergies and were diagnosed later with sesame allergy. Therefore, it seems likely that patients were not consuming any of the eliminated foods prior to initiation of elimination diet.

We then examined reasons for initiation of elimination diet for each of the eliminated foods. A previous reaction was the most common reason accounting for elimination of milk (55%), but was much less frequent (20%-30%) in the case of most other foods. Elimination of individual tree-nuts was done in >40% of cases due to a fear of cross contamination by another tree-nut or peanut to which the patient reacted to, while a reaction to the same tree-nut was documented in only 5.9% of the cases (**Fig 1a**). In many patients (35% – 80%), sensitization only (defined as SPT/sIgE $\geq$ grade 1) with no documented reaction, was the reason for elimination.

SPT and sIgE performed when patients' allergy was first diagnosed were available in 51/60 patients and for a total of 320 food allergens (**Fig 1b**). While for most allergens tested, SPT or sIgE were at grade 2-3 levels (SPT wheal size >4 mm or sIgE >3.5 kIU/L), many patients had absent or low sensitization. In the case of tree-nuts, SPT/sIgE were negative in almost 25% of the cases, and additional 32% were at grade 1 levels (**Fig 1b**). A total of 47 patients were diagnosed with atopic dermatitis (AD) or egg allergy in infancy. In 15 of those, peanut sensitization in infancy was within the inclusion criteria for the LEAP study and 7 (46%) had peanut allergy at study entry. To include only patients with more severe form of AD, we excluded patients whose AD resolved by study entry. A total of 34 patients were categorized as

severe atopic dermatitis or had egg allergy. In 10 of those, peanut sensitization in infancy was within the entry threshold for the LEAP study and 5 (50%) had peanut allergy at study entry.

Of the 50 patients who eliminated peanut from the diet, 6 (12%) eliminated soy due to sensitization only. Of those, 4 patients resumed soy consumption later in life with no adverse effects. Of the 2 patients that were still eliminating soy at study entry, 1 was found allergic to soy and the other was not challenged because of minimal sensitization and is likely not allergic. This data suggest that unlike peanuts and tree-nuts, elimination of soy is less likely to lead to soy allergy.

A reaction, either before the diagnosis was made or as a result of an accidental exposure later in life, occurred in 76% of milk-allergic patients, but in only 30-40% in the case of most foods and in only 14.5% of the children eliminating tree-nuts (**Table 2**). No significant difference was noted in the severity of reactions experienced to the different foods, as measured in the percentage of reactions treated with injectable epinephrine. Reactions due to accidental exposures to foods eliminated solely on the basis of sensitization or cross-contamination fear were experienced for walnut by 10/52 patients (19.2%, 2 required epinephrine), peanut – 6/37 (16.2%, 1 required epinephrine), almond – 1/48 (2%, no epinephrine required), cashew – 12/50 (24%, 4 required epinephrine), hazelnut – 0/58, pecan – 3/56 (5.4%, 2 required epinephrine), pistachio – 4/55 (7.3%, 2 required epinephrine), milk – 7/14 (50%, 5 required epinephrine), egg – 5/23 (21.7%, 1 required epinephrine), soy – 1/7 (14.3%, no epinephrine required), sesame – 3/17 (17.6%, no epinephrine required), and wheat – 0/3. Of the few, OFC reported by the patients to be previously performed by local

allergists at time of first allergy evaluation, most were negative. Re-introduction of eliminated food was relatively frequent (50-60%) among milk, soy and wheat allergic patients but much lower in the case of egg and lowest for sesame, peanut and tree-nuts (**Table 2**).

When examining the different tree-nuts separately, we found that a reaction led to the diagnosis of cashew allergy more often than for other tree-nuts, but even for cashew it accounted for only 14%, and the difference from other tree-nuts was not statistically significant (**Fig 2a**). Interestingly, in this cohort of multiple-food allergic patients, a reaction as a reason for initiating elimination was documented in only a single patient in the case of almond and in none in hazelnut (**Fig 2b**). SPT or sIgE levels were comparable for most tree-nuts (**Fig 2b**). However, SPT/sIgE levels for cashew, pistachio and walnuts were higher compared to other tree-nuts. That difference was statistically significant only compared to almonds (**Fig 2b**). While a reaction, either before the diagnosis was made or as a result of an accidental exposure later in life, was not frequent in all those with tree-nut allergies as a group, it occurred significantly more in the case of cashew (34%) and walnut (26%) compared to most other nuts (0-12%) (**Table 3**).

Finally, patients' SPT/sIgE levels were compared, between levels from the time patients were first diagnosed and current levels obtained on enrollment (available for 252 allergens). While no significant differences in SPT/sIgE grades were noted from time of diagnosis to time of enrollment for egg, milk, and sesame, grades were significantly higher on enrollment for peanut ($p=0.001$) and tree-nuts ($p<0.001$) (**Fig 3**). Of the 41 initially negative SPT/sIgE to tree-nuts, 27 became positive at enrollment (8

became grade 1, 10 grade 2, and 9 grade 3). Significant increases in the rate of grade 2-3 sensitization level was noted for: almond - from 16% to 79%, $p<0.001$; cashew - from 63% to 91%, $p=0.017$; hazelnut, from 48% to 81%, $p=0.017$; and pistachio – from 70% to 100% ($p=0.029$) (**Fig 3**).

OFCs performed at present for foods that were still eliminated, and fulfilling inclusion criteria, were positive for most foods: cashew (n=46 of 47), pistachio (n=42/42), hazelnut (n=30/42), walnut (n=32/35), pecan (n=29/30), almond (n=10/21), peanut (n=36/41), egg (n=19/19), milk (n=14/16), sesame (N=11/14), and soy and wheat (n=2/2 each).

DISCUSSION

The aim of this study was to examine “real life” approaches for food elimination in multiple food allergic-patients. We found that elimination of tree-nuts was unique in several aspects. First, a documented reaction was rare in the case of tree-nuts and their elimination was often based on fear of cross-contamination with another allergenic food. Second, overuse of allergy testing might lead to the diagnosis of multiple sensitizations, often minimal, leading in turn to unnecessary elimination diet early in life. Sensitization levels increased significantly years later, for peanut and tree-nuts in particular, and most OFCs performed at present were positive, suggesting that some tree-nut allergies developed during the period of elimination diet.

Certain scenarios exist in which the consensus recommendation, to diagnose food allergy based on a previous reaction or a positive OFC, becomes controversial. For example, some recommend avoidance of all tree-nuts by young children with peanut allergy because of practical concerns about cross-contamination (9). Others claim that a child with peanut allergy who is not allergic to tree-nuts should not be required to avoid individual tree-nuts, hypothesizing that oral exposure to a certain food enables acquisition of tolerance to it (21). A similar controversy exists in patients with a single tree-nut allergy with respect to avoidance of other tree-nuts (22). Infants with atopic dermatitis comprise another group of patients around which controversy exists. While food allergens are considered a significant trigger for atopic dermatitis in 30%-40% of patients, some guidelines advise to avoid routine testing in such children before introducing highly allergenic foods, such as milk, egg, or peanut into their diet (10, 23). However, children with AD without IgE-mediated food allergy might develop life-threatening food allergy following elimination of certain foods from the diet (7). Our

study demonstrates that OFCs were rarely performed in this group of multiple food-sensitized patients despite the fact that acute reaction was not documented for most eliminated foods. This suggests that overuse of allergy testing by pediatricians and allergists, might lead to over-diagnosis of food sensitizations, particularly in patients with AD. Once sensitization is documented, multiple OFCs are difficult to perform resulting in extensive elimination diet.

A SPT wheal size and sIgE level thresholds that would predict a positive food challenge have been reported for some foods (peanut, egg and milk) but attempts to provide similar predictive values for other foods in general, and specifically for tree-nuts, have failed (4, 9, 24). While a negative SPT provides useful information in ruling out IgE-mediated allergy to a specific food, a negative sIgE does not (9, 24-25). SPT/sIgE levels in many of our patients, and particularly in the case of tree-nuts, were negative, or between 0.35 to 3.5 kU/L (much lower than the threshold levels used for milk, egg or peanut for predicting a positive OFC). Therefore, many of the foods eliminated, particularly tree-nuts, might not have been allergenic at first.

Compared to other foods, SPT/sIgE levels of peanuts and tree-nuts increased significantly from initial diagnosis to the time patients were enrolled to the study. Moreover, many initially negative SPT/sIgE to peanut and tree-nuts were positive on enrollment. This may reflect the fact that peanut and tree-nuts allergy is less likely to resolve with time compared to other foods (5, 26-27). Alternatively, it could reflect the development of allergy in some patients who were only slightly sensitized. The high rate of atopy in our patients (80% had a history of atopic dermatitis and all had at least one food allergy) is similar to the population studied by Lack et al in which elimination

of peanuts from the diet resulted in increased risk of developing IgE-mediated peanut allergy (15). In our study, the rate of development of peanut allergy in patients with AD or egg allergy was higher (50%) compared to the 34% found in the LEAP study for patients with positive SPT to peanuts. However, this is not surprising given the fact that our group of patients was a selective group with additional food allergies. Thus, tree-nut elimination in these high-risk patients appears to have a similar effect.

The retrospective design of this study and its reliance on parents' memories limit our findings. However, in most cases, the data, including physician notes, SPTs and sIgE levels, was obtained directly from patients' medical records, providing additional support to the history obtained. In addition, this cohort comprised a selected group of patients with high levels of sensitization to multiple foods and high rate of positive OFC's as a result. Our findings should therefore be used to spark further investigations of additional less selected patients before general recommendations could be made.

The grading system we used for combining the SPT and sIgE levels is somewhat arbitrary and might be interpreted differently for each food, but it is based on previous studies. For example, an SPT wheal of <1 mm vs. 1-4 mm vs. >4 mm was used as the cutoff in the LEAP study and the SPT thresholds predictive of a positive OFC are >8mm for most foods (9, 15, 24, 28). The sIgE was graded based on the ImmunoCAP grading.

In summary, the present study provides a detailed description of reasons for initiating an elimination diet in a well-defined selected group of multiple food-allergic patients. This study raises several points. First, compared to most foods, elimination of tree-nuts was based on low probability of actual allergy, without a previous reaction to

the eliminated food, with low or even negative sensitization, and without performing an OFC. Second, sensitization levels, especially for tree-nuts, increased over time, and most patients had OFC-proven food allergy years later, suggesting that these food allergies developed over time.

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FIGURE LEGENDS

Figure 1. Triggers for elimination and baseline SPT or sIgE individual foods.

Reasons for elimination **(a)** and baseline SPT and sIgE levels **(b)** (grade 0; SPT=0 and sIgE<0.35, grade 1; $1 \leq \text{SPT} \leq 4$ or $0.35 < \text{sIgE} \leq 3.5$, grade 2; $5 \leq \text{SPT} \leq 8$ or $3.5 < \text{sIgE} \leq 17.5$, and grade 3; SPT>8, sIgE>17.5) to each food, were compared and Bonferroni correction applied. * Statistically significant differences were found between tree-nuts vs. egg, milk, peanut, sesame or wheat **(a)** and between tree-nuts vs. milk or sesame **(b)**.

Figure 2. Triggers for elimination and baseline SPT or sIgE for individual tree-nuts.

Reasons for elimination **(a)** and baseline SPT/sIgE levels **(b)** (grade 0; SPT=0 and sIgE<0.35, grade 1; $1 \leq \text{SPT} \leq 4$ or $0.35 < \text{sIgE} \leq 3.5$, grade 2; $5 \leq \text{SPT} \leq 8$ or $3.5 < \text{sIgE} \leq 17.5$, and grade 3; SPT>8, sIgE>17.5) to each tree-nut were compared and Bonferroni correction applied. * Statistically significant differences were found between almond vs. cashew, pistachio or walnut **(b)**.

Figure 3. Change in SPT/sIgE grade from time of diagnosis to study enrollment.

Past SPT/sIgE grades from the time patients were diagnosed (light blue) were compared to their present levels (orange) for each individual food and for each patient. Grey represents overlapping values from both time points. * Statistically significant increases were noted for peanut, almond, cashew, hazelnut and pistachio (see text for details).

Table 1: Demographics of the study population

Variable (n=60)		Mean
Age (y)		8.6±3.1
Male gender		30 (50%)
Race ^a	White	41 (68%)
	African American	2 (3.3%)
	Asian	28 (47%)
	Other	3 (5%)
Number of Food items ever eliminated from diet		8±1.7
Atopic dermatitis	diagnosed	46 (77%)
	Age at diagnosis	0.85±1.5
	Resolved #	19 (41%)
	Age of resolution	2.5±2.2
Asthma	Total	29 (48%)
	Age at diagnosis	3.2±2.8
Allergic rhinitis	Total	45 (75%)
	Age at diagnosis	4±2.2
Family history	Allergic rhinitis	57%
	Asthma	25%
	Food allergy	30%
	Eczema	18%

^a Numbers add up to >60 because some subjects self-identify with >1 race

Table 2: Characteristics, of foods initially eliminated from patients' diet

Variable		Tree nuts	Peanut	Milk	Egg	Soy	Sesame	Wheat
Ever eliminated, n		337	50	29	30	9	23	5
Age at elimination		1.2	1.1	0.8	1.0	1.0	2.0	0.8
Median, range (y)		0.1-9	0.3-8	0.1-1.3	0.3- 2	0.3-9	0.3-11	0.3-1
Male gender		51%	50%	62%	67%	56%	74%	80%
Race	White	71%	68%	69%	77%	78%	74%	100%
	Asian	46%	50%	45%	37%	44%	35%	20%
	Other	6.8%	6%	10%	13%	0%	8.7%	40%
Reaction ever [*]		14%	38%	76%	40%	33%	39%	40%
Reaction - skin ^a		79%	65%	74%	76.9%	67%	89%	50%
Reaction - GI ^a		49%	61%	52%	53.8%	67%	11%	50%
Reaction - resp. ^a		39%	22%	39%	38.5%	33%	11%	0
Reaction - Epi ^a		24%	12%	17%	25%	33%	0	0
OFC ever ^{**}		16%	18%	43%	43.3%	44%	22%	60%
Positive OFC		5/53	2/9	2/13	4/13	0/5	0/5	1/4
Food re-introduction ^{***}		14%	12%	48%	30%	56%	17%	60%
Current elimination, n		289	44	15	21	4	19	2

P value <0.00238 (after applying Bonferroni correction) is considered significant

^{*} Significant differences between tree nuts vs. egg, milk or peanut and between peanut vs. milk

^{**} Significant differences between tree nuts vs. egg and milk

^{***} Significant differences between tree nuts vs. milk and between peanut vs. milk

^a Refers to initial reaction and the percentage is of # of patients with reactions

Table 3: Characteristics of tree nuts eliminated from patients' diet

Variable		Almond	Cashew	Hazelnut	Pecan	Pistachio	Walnut
Ever eliminated, n		47	58	58	58	58	58
Male gender		55.3%	50%	50%	50%	50%	50%
Age at diagnosis		1.2	1.1	1.2	1.2	1.2	1.2
Median, range (y)		0.3-8	0.1-8	0.1-9	0.3-9	0.1-9	0.1-9
Race	White	74.5%	70.7%	70.7%	70.7%	70.7%	70.7%
	Asian	44.7%	46.6%	46.6%	46.6%	46.6%	46.6%
	Other	6.4%	6.9%	6.9%	6.9%	6.9%	6.9%
Reaction ever [*]		4.3%	34.5%	0	8.6%	12.1%	25.9%
Reaction - skin ^a		100%	78.9%	n/a	80%	71.4%	78.6%
Reaction - GI ^a		50%	60%	n/a	60%	57.1%	26.7%
Reaction – resp. ^a		0	40%	n/a	60%	28.6%	40%
Reaction - Epi ^a		0	25%	n/a	40%	28.6%	20%
OFC ever ^{**}		31.9%	7%	15.5%	15.5%	8.8%	19%
Positive OFC		0/15	1/4	1/9	1/9	1/5	1/11
Food re-introduction ^{***}		34%	5.2%	12.1%	13.8%	8.6%	15.5%
Current elimination, n		31	55	51	50	53	49

P value <0.0033 (after applying Bonferroni correction) is considered significant

^{*} Significant differences between cashew vs. almond, hazelnut, and pecan and between walnut vs. almond and hazelnut

^{**} Significant differences between cashew vs. almond

^{***} Significant differences between almond vs. cashew and pistachio

^a Refers to initial reaction and the percentage is of # of patients with reactions





