

きるようにするためには、今後、興味を持てる公正な情報提供ツールの開発、情報伝達システムの整備、教育現場等を介した正しい知識や情報の扱い方の習得が必要であると考え

E. 結論

幼児を持つ保護者(女性)を対象として、栄養や食に対する知識とその情報源、サプリメントの利用との関連を把握するためのアンケート調査を行った。その結果、幼児のサプリメント(錠剤・カプセルに限定)の利用経験率は9.8%であった。幼児の保護者は、5大栄養素等、基礎的な知識は十分にあるが、国の制度・調査については知らない者が多く、テレビ・インターネットの情報を参考としており、政府機関の発行物はあまり参考にされていなかった。以上から、公的もしくは専門機関からのより積極的な情報提供の必要性が示唆された。

F. 研究発表

1. 論文発表

1) Yoko Sato, Azumi, Yamagishi, Yoko Hashimoto, Nantiga Virgona, Yoshiharu Hosiyama, Keizo Umegaki: Use of Dietary Supplements among Preschool Children in Japan. J Nutr Sci Vitaminol. 55:317-325, 2009

2. 学会発表

なし

3. その他

なし

G. 知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

表 1. 知識問題 (○×形式で回答)

項目
<p><5 大栄養素></p> <p>1 炭水化物(糖質)はエネルギー源だ</p> <p>2 ビタミンはからだの機能を調整するはたらきがある</p> <p>3 脂質は、細胞膜の構成成分として重要なはたらきがある</p> <p>4 鉄は血液をつくるものになる</p> <p>5 たんぱく質は、筋肉や皮膚、骨などからだの組織をつくる</p>
<p><食品と栄養素></p> <p>6 肉には、鉄だけでなくビタミンも含まれている</p> <p>7 ごはんは、たんぱく質の供給源としても重要だ</p> <p>8 レバーの焼き鳥には DHA(ドコサヘキサエン酸)が含まれている</p> <p>9 肉や魚を食べると、アミノ酸を摂取できる</p> <p>10 切り干し大根の煮物にはカルシウムや鉄が含まれている</p>
<p><摂取量の考え方></p> <p>11 コレステロールは出来る限り食事から排除すべきだ</p> <p>12 ビタミンはからだに必要な栄養素なので、たくさん摂取するほどよい</p> <p>13 10g のオリーブ油は 10g のバターより低カロリーだ</p> <p>14 うすくち醤油 15g(大さじ 1)は、こいくち醤油 15g(大さじ 1)よりも食塩含有量が少ない</p> <p>15 「カロリーゼロ」「ノンカロリー」と表示された食品なら、いくら食べても太らない</p>
<p><国の制度・調査></p> <p>16 食事摂取基準で示された栄養素の量は、毎日必ず摂取 しなければならない</p> <p>17 栄養機能食品は、製品ごとに国が審査し、許可している</p> <p>18 栄養機能食品に認められている成分は、ビタミンとミネラルだけである</p> <p>19 特定保健用食品(通称 トクホ)は、国が認めた食品なので、必ず効果がある</p> <p>20 国民健康・栄養調査の結果では、現代の子ども達は栄養不足といえる</p>
<p><サプリメント></p> <p>21 サプリメントと呼ばれる食品の有効性・安全性は、製品によって大きな違いがある</p> <p>22 「ブルーベリーは目にいい」には、実は科学的根拠があまりない</p> <p>23 自然の食品から抽出した成分であれば、安全だ</p> <p>24 ホルモンはからだに元々あるものなので、飲んでも安全だ</p> <p>25 偏食や少食の子どもは、栄養不足にならないように、サプリメントを使用するのが望ましい</p>
<p><食品の安全></p> <p>26 天然素材のサプリメントには、食品添加物は使用されていない</p> <p>27 加工食品は、食品添加物を使用していない方が安全だ</p> <p>28 食品添加物は、ほとんど使用基準値の上限に近い量が使われている</p> <p>29 残留農薬を落とすため、野菜は洗剤で洗って使うとよい</p> <p>30 浄水器を通した水はきれいなので、長く保存できる</p>

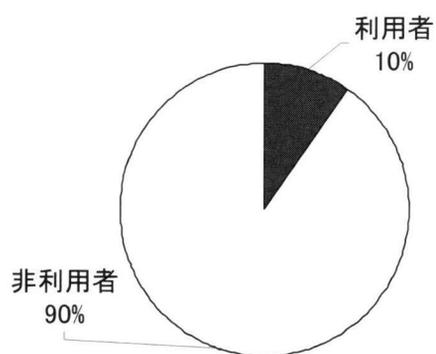


図 1. 幼児のサプリメント(錠剤・カプセルのみ)の利用経験者割合

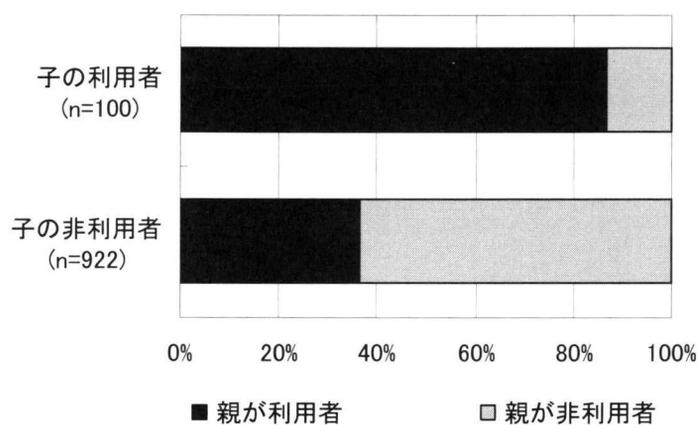


図 2. 子どものサプリメント利用と親のサプリメント利用の関連

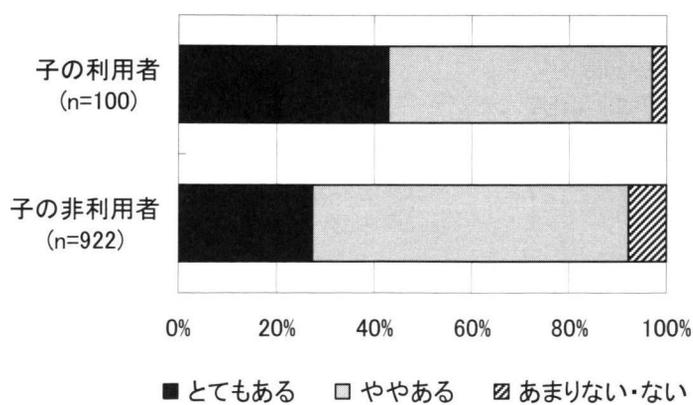


図 3. 子どものサプリメント利用と親の栄養への興味の関連

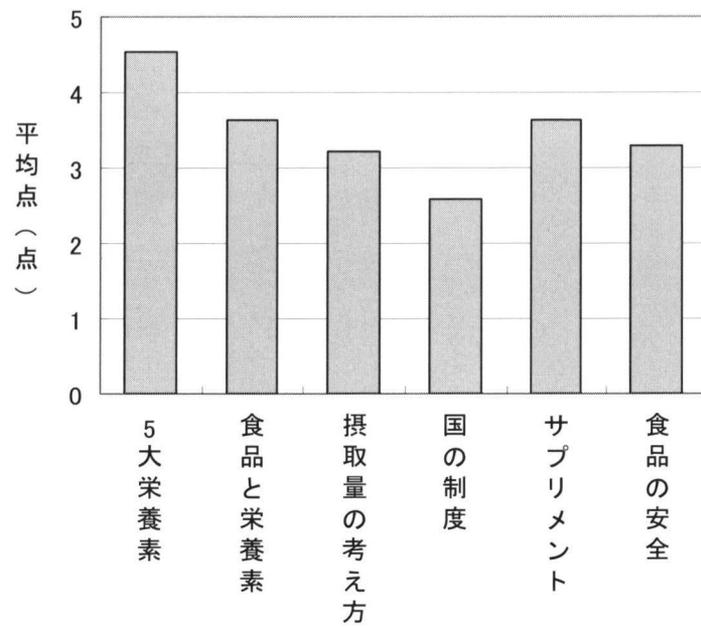


図 4. カテゴリー別平均点(各 5 点満点)

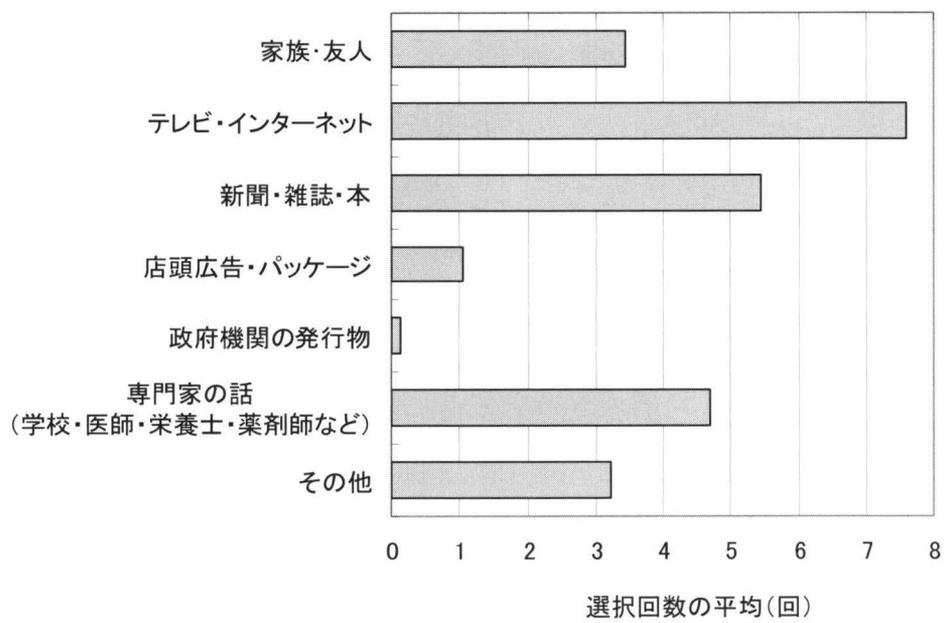


図 5. 判断の参考とした情報源

厚生科学研究費補助金(食品の安心・安全確保推進研究事業)
(分担)研究報告書
健康食品の情報提供システム体制の構築と安全性確保に関する研究
健康食品の摂取に伴う健康被害の因果関係判定法の検討

研究分担者 山田 浩 静岡県立大学薬学部
研究協力者 松本 圭司 浜松医科大学薬剤部
加藤 竜維 静岡県立大学薬学部
朴 美貞 静岡県立大学薬学部
小菅 和仁 静岡県立大学薬学部

研究要旨

健康食品の摂取に伴う健康被害として報告される情報は種々雑多であり、その情報を正確に把握し因果関係の評価判定を行うことは極めて難しい。また、その健康被害の因果関係を科学的に吟味するための臨床上有用な方法論も、未だ確立されていない。我々は今までに、医薬品の有害事象の因果関係判定に利用されているアルゴリズムを改変し、健康食品の摂取に伴う健康被害の因果関係判定への適用を試みてきたが、信頼性において十分といえない状況が存在した。本研究では、開発してきたアルゴリズムを再検討し、適用上の問題点を抽出し改良を加えることで、臨床現場で実際に遭遇する健康被害事例に応用可能な因果関係評価判定法の構築を試みた。

A. 研究目的

健康食品の摂取に伴う健康被害が生じた場合、その情報はドラッグストアや製造販売元への消費者からの相談、あるいは医療機関を受診し治療を受けた場合の診療録等を基に、保健所を介して厚生労働省に集約されていくが、その情報は種々雑多であり、正確に把握し因果関係の評価判定を行うことは極めて難しい。また、その健康被害の因果関係を科学的に吟味するための臨床上有用な方法論も、未だ確立されていない。我々は今までに、医薬品の有害事象の因果関係判定に利用されているアルゴリズムを改変し、健康食品の摂取に伴う健康被害の因果関係判定への適用を試みてきたが、信頼性において十分といえない状況が存在した。本研究では開発してきたアルゴリズムを再検討し、適用上の問題点を抽出し改良を加えることで、臨床現場で実際に遭遇する健康被害事例に応用可能な因果関係評価判定法の構築を試みた。

B. 研究方法

健康食品の摂取に伴う健康被害事例とし

D. 考察

て、ある特定の健康食品の摂取に伴う肝機能障害の症例報告を、MEDLINE 等二次資料データベースを利用して網羅的に抽出し、文献を収集した。その文献を、因果関係評価のために開発した評価票を適用して評価判定を行った。評価項目は 10 項目の質問から成り、その評価点の合計に基づき因果関係が強い順に、highly probable、probable、possible、remote の 4 段階にカテゴリ分類した。次いで評価結果を基に、評価票の適用上の問題点を抽出した。

C. 研究結果

抽出した健康被害事例 36 例の評価判定の結果、11 例が probable、25 例が possible にカテゴリ分類された。評価項目別では、全ての事例において「プラセボの投与による症状の出現」、「毒性域を確かめるための血中濃度測定」、「摂取量の増減による症状の変動」の項目に関する情報が得られなかった。健康食品の製品表示が不十分で、含有量や添加物の情報が不明なものも見られた。

健康食品は医薬品と比較し、健康被害との

因果関係を判断するための情報が少ない。特にプラセボ投与、血中濃度と毒性との関連、摂取量の増減による症状の変動といった評価項目に関する情報は得られにくい結果となったことから、これらの判断項目としての価値は低いと思われる。一方、健康食品の含有量、添加物といった製品情報は因果関係の判断に影響を与えることから、調査票に付与すべき内容と考える。

E. 結論

健康食品の摂取に伴う健康被害の因果関係判定には、医薬品と異なる判断が要求される部分がある。今後、健康食品の特殊性を考慮した因果関係判定法を確立し、臨床現場から得られる健康食品の摂取に伴う健康被害の多様な事例を入手して評価判定を行うことにより、その評価法の有用性を明らかにすべきと考える。

F. 研究発表

1. 論文発表

1) 山田浩、松本圭司、清水雅之、熊谷翼、渡邊崇之、近都正幸、朴美貞、小菅和仁、川上純一、梅垣敬三：健康食品摂取と健康上の有害事象の因果関係を評価するためのアルゴリズムの提案。臨床薬理 40(4)：163-168, 2009.

2) 山田浩、山田薫。「肥満と糖尿病の薬物療法」Q&A/ダイエット関連健康食品の有害事象は？ダイエット関連健康食品の有害事象について教えてください。肥満と糖尿病：8(2)：192-193, 2009.

2. 学会発表

1) 加藤竜維、清水雅之、渡邊崇之、小菅和仁、望月亜希子、岩崎剛士、神戸宏憲、坂本達一郎、河原崎貴伯、梅垣敬三、山田浩。健康食品と医薬品の併用に伴う有害事象の因果関係評価判定のための評価票の検討。第30回日本臨床薬理学会年会、横浜、2009年12月3-5日

2) 渡邊崇之、吉川俊博、金子貴則、朴美貞、小菅和仁、梅垣敬三、山田浩。茶カテキンおよび茶摂取が血中脂質へ及ぼす影響-ランダム化比較試験を対象としたメタアナリシス研究-。第30回日本臨床薬理学会年会、横浜、2009年12月3-5日

3) 朴美貞、加治慎也、藤本雅宣、松下久美、北川俊朗、小菅和仁、山田浩。学童のインフ

ルエンザ罹患状況と予防対策に関するアンケート調査：緑茶との関連。第30回日本臨床薬理学会年会、横浜、2009年12月3-5日

4) 小菅和仁、寺尾昭宏、木俣美津夫、鈴木留美子、浅野正宏、鈴木千恵子、吉田雅行、浜口弘睦、小國伊太郎、山田浩。カテキン含有マスクによるインフルエンザ予防の検討。第30回日本臨床薬理学会年会、横浜、2009年12月3-5日

3. その他

なし

G. 知的所有権の取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

別紙 4 研究成果の刊行に関する一覧表

書籍

著者氏名	タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
信川益明	食品保健と健康科学	細谷憲政、林裕造、上野川修一	食品保健の科学	丸善	東京	2010	291-305

雑誌

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yoko Sato, Azumi Yamagishi, Yoko Hashimoto, Nantiga Virgona, Yoshiharu Hoshiyama, Keizo Umegaki 山田浩、山田薫	Use of Dietary Supplements among Preschool Children in Japan. ダイエット関連健康食品の有害事象は？ダイエット関連健康食品の有害事象について教えてください。	J Nutr Sci Vitaminol. 肥満と糖尿病	33 8(2)	317-325 192-193	2009 2009
山田浩、松本圭司、清水雅之、熊谷翼、渡邊崇之、近都正幸、朴美貞、小菅和仁、川上純一、梅垣敬三	健康食品摂取と健康上の有害事象の因果関係を評価するためのアルゴリズムの提案	臨床薬理	40(4)	163-168	2009

Use of Dietary Supplements among Preschool Children in Japan

Yoko SATO¹, Azumi YAMAGISHI², Yoko HASHIMOTO³, Nantiga VIRGONA^{1,4},
Yoshiharu HOSHIYAMA⁵ and Keizo UMEGAKI^{1,*}

¹National Institute of Health and Nutrition, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-8636, Japan

²Yamagata University, 1-4-12 Kojirakawamachi, Yamagata, Yamagata 990-8560, Japan

³Akikusa Gakuen Junior College, 1789 Izumicho, Tokorozawa, Saitama 359-1112, Japan

⁴Herbal Medicines Research and Education Centre, Faculty of Pharmacy A15,

The University of Sydney, NSW 2006, Australia

⁵University of Human Arts and Sciences, 1288 Magome, Iwatsuki, Saitama 339-8539, Japan

(Received October 22, 2008)

Summary This study was conducted to examine the characteristics and use of dietary supplements by preschool children in Japan. A survey was conducted among 2,125 parents of preschool children to discover the status of dietary supplement use and their attitudes towards supplement use by their children. Logistic regression models were used to determine which characteristics predict supplement use in this population. For detailed characterization, child supplement users were also categorized as either the users of vitamins and minerals only or the users of other supplement components. For parents of non-user children, the parent's knowledge and attitudes toward supplements for children were investigated. Fifteen percent of children had used dietary supplements. Two parent-related factors were especially important, the frequency with which they referred to nutritional labels and their own supplement use, which had a significant encouraging effect on their children's supplement use. The parents of child supplement users showed limited awareness of the government system concerning diet and food, placed safety over efficacy, selected products with natural ingredients, and did not seek consultations with professionals. These parents, especially those who were aware of the specially designed supplements for children, exhibited positive responses to supplement use by their children. It is likely that parents' knowledge and attitudes toward dietary supplements and nutrition have a striking effect on their children's use of supplements. Unfortunately, their knowledge at present was less than satisfactory. More accurate information on nutrition, dietary intake and dietary supplements must be disseminated.

Key Words dietary supplements, preschool children, Japan

Foods with health-promoting effects have been increasingly desired in recent years, and dietary supplements have been attracting attention in many countries throughout the world. In Japan, the market for dietary supplements has grown rapidly with the distribution of numerous products (1, 2), but the environment surrounding dietary supplements is not well-organized. There is no clear definition of dietary supplements in Japan, and individuals apply their own interpretation of these products. However, it is understood that in general the term "supplement" corresponds to what are called dietary supplements in the United States.

The Japanese government regulates supplements and functional foods in two categories (3). One is Food for Specified Health Uses (FOSHU), and the other is Food with Nutrient Function Claims (FNFC), which contains vitamins and minerals that have accumulating scientific evidence for their safety and efficacy as in the Dietary Reference Intakes (4), and corresponds to

dietary supplements in the United States. However, most of the products on the market are neither FOSHU nor FNFC and exist as general foods, without clear monitoring of their number and usage, which often contain ingredients that lack scientific evidence for their safety and efficacy (5, 6). The Japan Health Food and Nutrition Food Association, an organization that represents the associated industries, has voluntarily prepared safety standards to guarantee the quality of such foods and places a JHFA (Japan Health Food Authorization) mark on their products. Unfortunately, the market for products with the JHFA mark seems to be small.

The number of adult supplement users in Japan has recently become larger and larger, as in the United States and other developed countries (7–10). According to recent studies in various areas of Japan, 55% of men and 61% of women have used supplements (10). The purpose of their use was for health maintenance, nutritional replenishment, beauty, and the prevention of illness. The respondents favored capsules and tablets; obtained their information from television, the Internet,

*To whom correspondence should be addressed.

E-mail: umegaki@nih.go.jp

merchandize fliers, and family or relatives; and purchased the supplements at pharmacies, drug stores, or through the Internet (11–14). Furthermore, the prevalence of supplement use is highest in the elderly; women; and individuals with a lower BMI, greater physical activity, a higher frequency of eating out, or high stress levels (10, 15).

Supplements are enriched with specific components such as vitamins, minerals, and other natural substances. The use of supplements would be beneficial for supplementation of a substance when its dietary intake is inadequate; however, adverse effects may be induced due to inappropriate use, the use of substances with little scientific evidence for their safety and efficacy, intake for disease prevention/curing without consultation with health professionals, and the use by high-risk-groups such as children and pregnant women.

Children, especially young children, are more vulnerable to the adverse effects of substances like dietary supplements. Therefore, taking supplements should be considered high risk for young children. In addition, young children are in the process of forming healthy dietary habits, so reliance on supplements may result in a disregard for the importance of healthy daily eating habits. In the United States where the use of supplements by adults became popular earlier than in Japan, it has been reported that supplement use by children is common and is being extended to infants (16–23). In those studies, it was shown that about 30 to 50% of children take supplements and that the factors that affect their use are families with higher incomes, only one child, or dietary problems, parents with a high education level, and parent's use of supplements. However, it remains unclear which factors enhance the use of supplements by children.

It is anticipated that the use of supplements by children will increase in Japan. However, there are no reports on supplement use by young children in Japan. Thus, in this study a questionnaire was administered to observe the current status of supplement use and the characteristics and factors that relate to the use of supplements in preschool children.

SUBJECTS AND METHODS

Subjects. The subjects of the survey were 2,125 parents of children attending 21 cooperating kindergartens and day-care centers (7 kindergartens and 14 day-care centers) located in 7 prefectures (Aomori, Yamagata, Ibaraki, Tochigi, Chiba, Saitama, and Kagawa) from May through September 2007. In Japan, kindergartens and day-care centers provide pre-school care and educational services. The former are schools for children 3 y of age or older where they are cared for, for an average of 4 h a day. The latter are child welfare facilities where infants and young children, even those younger than 12 mo of age, are taken care of while their parents are working. They are generally cared for for 8 h a day, which may be adjusted to suit their parents' work schedules. Responses were obtained from 1,533 parents (effective recovery rate: 72.1%), among

which 96.5% were women, and 72.6% were in their 30s. Completion of the survey was considered informed consent. This study was conducted with the approval of the Research Ethics Committee of the National Institute of Health and Nutrition of Japan.

Questionnaires. Our descriptive study used an anonymous, self-reported survey. The questionnaire was distributed at kindergartens and day-care centers. Arrangements were made to have the sheets collected at each kindergarten or day-care center and mailed to the party conducting the survey. The questionnaire topics were as follows.

The characteristics of the parents and their children were obtained including: The parents' sex and age (in decades), the children's age, number of siblings, birth order, and social environment (kindergarten or day-care center). Home income and parent's education level were not investigated because we believe that such questions would have decreased the recovery of responses.

Parents' and children's dietary supplement use: Considerable confusion is unavoidable because there is no set definition for dietary supplements in Japan. In the current survey, they were defined as those food substances that were in a tablet, capsule, powder, granule, extract, or chewable tablet form, according to the definition similar to dietary supplements in the United States. The use of supplements by parents and children was defined by the following four categories: "daily use," "occasional use," "past use," and "have never used." Later in the study, the last category was renamed the "supplement non-users" while the others were grouped as "supplement users."

Parents' attitudes towards diet: Using The National Health and Nutrition Survey in Japan, 2004 (24), questions were posed on dietary problems and the desire for improvement as an expression of the parents' awareness of the issues concerning their children's diet. The extent of the use of nutritional labels was used to interpret the parents' interest in diet. To assess their level of knowledge about food, questions were asked about their awareness of the standard dietary intake and the dietary balance guide. This standard dietary intake refers to the "Dietary Reference Intakes for Japanese, 2005" (4), which was formulated by the Ministry of Health, Labour, and Welfare of Japan. This standard is designed to show the optimum amounts of energy and five types of nutrients for Japanese to consume according to their gender and age to maintain and promote their health, as well as to prevent energy and nutrient deficiencies, life-style-related diseases, and disorders due to excessive intake. The dietary balance guide (25) was prepared by the Ministry of Health, Labour, and Welfare and the Ministry of Agriculture, Forestry, and Fisheries of Japan: it shows an ideal diet and estimates the amounts of food to be consumed, with easy-to-understand illustrations so that the Japanese population will learn the basis of good eating habits.

The state of supplement use among children: The following topics were addressed with those children who

Table 1. Logistic regression analysis of characteristics associated with the number of children using supplements.

Characteristic	Children ^a			Characteristic considered ^b		
	Supplement users ^c % (n)	Supplement non-users % (n)	p value	Odds ratio	95% CI	p value
Total	15.0 (228)	85.0 (1,288)				
Age ^d	4.38±1.0	4.16±1.3	<0.01	1.13	0.98–1.31	ns ^e
Number of siblings ^d	1.98±0.7	1.97±0.7	ns			
Birth order			ns			
First	55.1 (125)	55.0 (705)		0.96	0.55–1.68	ns
Second	33.9 (77)	34.3 (440)		0.87	0.49–1.53	ns
Third or later	11.0 (25)	10.6 (136)		1.00		
Social environment			<0.01			
Kindergarten	71.9 (164)	59.3 (764)		1.51	1.03–2.22	<0.05
Day care center	28.1 (64)	40.7 (524)		1.00		
Area ^f			ns			
Tohoku	41.2 (94)	42.3 (545)		0.86	0.34–2.15	ns
Kita-Kanto	33.3 (76)	33.9 (436)		1.04	0.43–2.53	ns
Kanto	21.1 (48)	18.6 (239)		1.13	0.44–2.87	ns
Shikoku	4.4 (10)	5.3 (68)		1.00		
Sex of interviewed parents			ns			
Male	3.1 (7)	2.6 (34)		2.07	0.80–5.32	ns
Female	96.9 (220)	97.4 (1,253)		1.00		
Age of parents			ns			
<30	9.7 (22)	13.8 (178)		0.90	0.46–1.74	ns
30–39	74.0 (168)	72.5 (932)		0.97	0.61–1.52	ns
≥40	16.3 (37)	13.7 (176)		1.00		
Dietary problems			ns			
Many	10.9 (24)	9.2 (117)		1.66	0.93–2.94	ns
Some	63.3 (140)	62.3 (789)		1.16	0.80–1.68	ns
Non	25.8 (57)	28.5 (361)		1.00		
Desire to improve			ns			
Wish to improve	68.4 (154)	63.0 (800)				
All right as I am	24.0 (54)	24.3 (309)				
Have not considered	7.6 (17)	12.7 (161)				
Use of nutritional labels			<0.01			
Always	13.2 (30)	7.9 (102)		2.62	1.32–5.20	<0.01
Occasionally	51.8 (118)	44.0 (566)		1.90	1.11–3.23	<0.05
Rarely	25.4 (58)	27.4 (352)		1.78	1.01–3.14	<0.05
Never	9.6 (22)	20.7 (266)		1.00		
Dietary reference intake			ns			
Aware of contents	17.4 (39)	18.8 (240)		0.74	0.41–1.34	ns
Have heard about it	69.6 (156)	65.9 (843)		1.11	0.69–1.79	ns
Do not know	12.9 (29)	15.4 (197)		1.00		
Dietary balance guide			ns			
Aware of details	19.7 (44)	19.0 (242)				
Have heard about it	56.5 (126)	55.7 (710)				
Do not know	23.8 (53)	25.3 (323)				
Parents' supplement use			<0.01			
Daily	24.0 (53)	9.7 (120)		13.55	6.75–27.21	<0.01
Occasional	44.3 (98)	24.4 (302)		9.61	5.00–18.49	<0.01
Past	26.2 (58)	35.3 (437)		4.14	2.12–8.09	<0.01
Never	5.4 (12)	30.6 (378)		1.00		

^a Categorical variables: p value calculated by χ^2 test. Continuous variables: p value calculated by t-test. The missing values were excluded.

^b Logistic regression analysis.

^c The users include "daily use," "occasional use," and "past use."

^d Mean ± SD.

^e ns: not significant.

^f Tohoku: Aomori and Yamagata, Kita-Kanto: Ibaraki and Tochigi, Kanto: Saitama and Chiba, Shikoku: Kagawa.

use supplements: how old were they when they began to take supplements, the types of ingredients in the supplements (Vitamin/Mineral and others), the form of the supplement, the purpose of their use, their source of information, the place where the supplements were purchased, what cautions were exercised when purchasing the supplements, and their impression of the effects of the supplement.

The attitudes of the parents of the non-supplement-using children toward supplements: The following questions concern those children who do not use supplements: the extent of knowledge of the parent about supplements that are specially prepared for children, the age at which the use of supplements should be approved, the probability of their future use, and their attitude towards supplement use by children.

Statistical analysis. The characteristics of the users of the children's supplements were compared against those of the non-users. The children using the supplements were divided into two groups: one that had experience of using only vitamins and minerals (the Vitamin-Mineral group) and one that had experience of using other components (the non-Vitamin-Mineral group), and a comparison was made based on the status of their use. To compare the parents' attitudes toward supplement use, those who did not give supplements to their children were stratified by the extent of their agreement with the concept of supplements for children. For inter-group comparisons, a *t*-test was performed for continuous variables, and the χ^2 test was used for categorical variables.

Logistic regression was performed to determine which factors (area, social environment, gender of the parent, age of the parent, age of the child, birth order, diet problems, use of nutritional labels, extent of awareness of dietary reference intakes, or parent's supplement use) predicted children's supplement use. These factors did not show any correlation in an evaluation of the multiple covariance among the tested variables, using Spearman's rank correlation coefficient ($\gamma < 0.4$). The data were analyzed using SPSS 15.0J for Windows and HALBOU 7, and the level of significance was set at $p < 0.05$.

RESULTS

Supplement use in parents and their children

The experience of supplement use by children was as follows: 2.1% ($n=32$) in the "daily use" group, 7.0% ($n=106$) in the "occasional use" group, 5.9% ($n=90$) in the "past use" group, and 85.0% ($n=1,288$) in the "have never used" group. Similarly, the experience of use by their parents was 11.8% ($n=173$) in the "daily use" group, 27.5% ($n=402$) in the "occasional use" group, 34.0% ($n=498$) in the "past use" group, and 26.7% ($n=391$) in the "have never used" group. These 4 groups of supplement use were indicative of the purchasing attitude of the parents; thus, the data were subjected to the Kruskal-Wallis test. The analysis revealed no difference among the 3 groups of "daily use," "occasional use," and "past use." Accordingly, the 3 groups

were designated as the "users" group and the "have never used" group was designated as the "non-users" group in the remaining part of the study.

Characteristics of dietary supplement users

Table 1 shows the characteristics of the children who use supplements. No significant differences were noted in terms of the number of their siblings, birth order, place of residence, gender or age of the parents. However, the mean age in children was significantly higher in the users than in the non-users ($p < 0.01$). The proportion of supplement users in kindergarten was also significantly higher than that in day-care centers ($p < 0.01$). In the parents' evaluation of their children's dietary habits and their desire to improve them, more than half admitted to the existence of many or some problems, and their wish to improve them. These parents' attitude, however, did not influence the children's use of supplements. The reference to nutritional labels by parents during dining out or food shopping was significantly higher in the child users than in the non-users ($p < 0.01$). Less than 20% of parents were aware of the Dietary Reference Intakes (4) and the Dietary Balance Guide (25), which provide basic information about nutrition and diet and were established by the Japanese government. Parents' awareness of this basic knowledge did not relate to the use of supplements by their children. There was a significant ($p < 0.01$) relationship between parents' and children's supplement use.

Multivariate regression analysis revealed that three characteristics were independent predictors of children's supplement use (Table 1). These included the affiliation of children, parents' use of nutritional labels, and parents' supplement use. In particular, the more often the parent referred to nutritional labels and the higher the amount of supplements the parents used, the more frequently their children took dietary supplements. The present study failed to show any correlation between birth order, the children's age, the parents' evaluation of their diet or their desire for improvement,

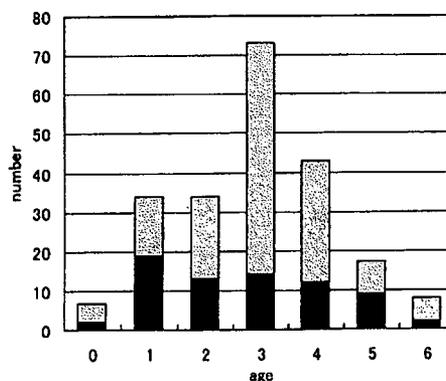


Fig. 1. Number and age of children that started using supplements: a comparison of two categories of supplements. □ Vitamin-Mineral Supplement group: mean \pm SD = 4.23 ± 1.574 y. ■ Non-Vitamin-Mineral Supplement group: mean \pm SD = 3.88 ± 1.736 y. $t = 1.464$; $p = 0.146$.

Table 2. Status of supplement use by children.

	Vitamin-Mineral Supplement group % (n)	Non-Vitamin Mineral Supplement group % (n)	p value ^a
Total	67.5 (154)	32.5 (74)	
Frequency of use			ns ^b
Past	43.5 (67)	31.1 (23)	
Occasional	45.5 (70)	48.6 (36)	
Daily	11.0 (17)	20.3 (15)	
Dosage form ^c			
Tablet	40.0 (58)	48.5 (32)	ns
Capsule	4.3 (6)	30.4 (21)	<0.01
Powder	6.2 (9)	15.9 (11)	<0.05
Granule	15.9 (23)	11.6 (8)	ns
Extract	0.7 (1)	1.4 (1)	ns
Chewable	55.2 (80)	43.5 (30)	ns
Purpose of use ^c			
Nutritional supplement	70.1 (101)	57.4 (39)	ns
Health promotion	20.8 (30)	41.2 (28)	<0.01
Disease prevention	12.5 (18)	35.3 (24)	<0.01
Body constitution	9.7 (14)	19.1 (13)	ns
Correcting constipation	7.6 (11)	4.4 (7)	ns
Physical strength	4.9 (7)	8.8 (6)	ns
Physical stamina	2.8 (4)	5.9 (4)	ns
Management of a chronic condition	1.4 (2)	2.9 (2)	ns
Observed/Noted at purchase ^c			
JHFA ^d mark (as a quality certificate)	12.1 (17)	6.0 (4)	ns
Extensively marketed	8.5 (12)	7.5 (5)	ns
Well-known manufacturer	24.1 (34)	14.9 (10)	ns
Natural materials	33.3 (47)	49.3 (33)	<0.05
Inexpensive	18.4 (26)	17.9 (12)	ns
Nutritional labels	41.8 (59)	43.3 (29)	ns
Without additives	35.5 (50)	40.3 (27)	ns
Non-allergenic	10.6 (15)	11.9 (8)	ns
Foods for Nutrient Function Claims	34.0 (48)	28.4 (19)	ns
Important points when purchasing			ns
Efficacy	9.7 (14)	7.4 (5)	
Safety	88.2 (127)	89.7 (61)	
Neither	2.1 (3)	2.9 (2)	
Consulted with: ^c			
Pharmacist	11.8 (17)	11.8 (8)	ns
Nutritionist	3.5 (5)	1.5 (1)	ns
Physician	6.3 (9)	10.3 (7)	ns
Store clerk	15.3 (22)	8.8 (6)	ns
Family and relatives	17.4 (25)	16.2 (11)	ns
Acquaintances and friends	17.4 (25)	29.4 (20)	<0.05
None	45.8 (66)	42.6 (29)	ns
Precautions for use ^c			
Observe specified quantity	74.3 (107)	71.6 (48)	ns
Do not take more than 2 types of supplements	11.8 (17)	13.4 (9)	ns
Eat regular meals	59.0 (85)	58.2 (39)	ns
Nothing in particular	10.4 (15)	6.0 (4)	ns
Felt efficacy			<0.05
Yes	37.9 (53)	53.7 (36)	
No	62.1 (87)	46.3 (31)	

^ap value calculated by χ^2 test.^bns: not significant.^cMultiple answers allowed within the category (percentage of those who selected).^dJHFA: Japan Health Food Authorization, which certifies the quality of health foods.

Table 3. Attitude of parents of non-supplement-using children towards supplement use.

	Awareness of supplements for children		p value
	Aware group % (n)	Unaware group % (n)	
Total	30.5 (359)	69.5 (818)	
Allowable age ^a	13.1 ± 5.7	14.7 ± 6.0	<0.01
Opinion of children's use ^b			<0.01
Allowable	19.0 (68)	12.1 (98)	
Only if absolutely necessary	70.3 (251)	74.4 (603)	
Should not be used at all	10.6 (38)	13.6 (110)	
Possible to give own child ^b			<0.01
Yes	44.6 (160)	32.2 (263)	
No	55.4 (199)	67.8 (554)	

^a Mean ± SD, p value calculated by *t*-test.

^b p value calculated by χ^2 test.

and the children's experiences with supplement use.

Details of supplement use by children

Sixty-eight percent of child supplement users ($n=154$) took vitamins and minerals only, and the remaining (32.5%, $n=74$) were users who had experience of non-Vitamin/Mineral supplements. The five most reported non-Vitamin/Mineral supplements were fish oil (44.6%), xylitol (10.8%), proteins (9.5%), herbs (8.1%), and vinegar (4.1%). More of the non-Vitamin/Mineral group than the Vitamin/Mineral group had started using supplements at one year old, but the mean age at first use was similar in both groups (Fig. 1).

The details of supplement use by children were compared with regard to the Vitamin/Mineral and non-Vitamin/Mineral groups (Table 2). The frequency of supplement use was most often described by both groups as "occasional," but a number of children responded "daily." The most frequently used forms of supplements were chewable or ordinary tablets in both groups. The capsules and powder forms were more popular in the non-Vitamin/Mineral group than in the Vitamin/Mineral group. Many products used were labeled "For children" or "May also be used by children," but some parents gave their children products "that were identical to those prepared for adults" (22.4%) or for which were "not certain about their suitability for children" (3.3%). Nutritional supplementation was the most prevalent purpose given by both groups. Unlike the Vitamin/Mineral group, health promotion and prevention of diseases were also frequent purposes given by those in the non-Vitamin/Mineral group. There were no significant differences between the two groups in the sources of information obtained; the major sources of which were over the counter (34.0%), acquaintances and friends (30.1%), and newspapers and magazines (12.9%).

The products were purchased mainly at pharmacies (41.7%) or via mail order (37.4%). Notable differences between the two groups were as follows: the presence of nutritional labels, the absence of food additives, and

foods with nutrient function claims (in descending order) were noted by the Vitamin/Mineral group, while the use of natural materials was frequently cited by those in the non-Vitamin/Mineral group. At the time of purchasing, both groups emphasized the importance of safety (more than 80%).

In giving supplements to children, most parents did not seek consultation from others, especially from health professionals such as pharmacists, nutritionists, or physicians. Any consultation, if it was sought, was from family and relatives, acquaintances, and friends, which were more prevalent consultants in the non-Vitamin/Mineral group than in the Vitamin/Mineral group ($p<0.05$). The precautions taken for use were "Observe the specified quantity" for more than 70%, and "Eat regular meals" for almost 60%. More parents in the non-Vitamin/Mineral group than in the Vitamin/Mineral group gained a feeling of the efficacy of the supplement used ($p<0.05$).

Attitude of parents of non-supplement-using children toward supplement use

Among the parents whose children were supplement non-users, 30.5% ($n=359$) were aware of the existence of supplements that have been specially designed for children. The former were designated as the "aware group" and the latter as the "unaware group," and these categories were used for further analysis (Table 3). The allowable age for using supplements ranged widely (1 to 60 y), with the mean age being significantly higher in the unaware group ($p<0.01$). More parents in the aware group than in the unaware group approved the use of supplements by children ($p<0.01$) and stated that they may give their children supplements in the future ($p<0.01$).

DISCUSSION

Dietary supplements, which are specific enriched components such as vitamins, minerals, and other natural substances, have received great attention worldwide. Such supplements allow the easy intake of a spe-

cific substance, but adverse effects may occur in cases of inappropriate use, especially in such use by young children, who are one of the high-risk-groups and therefore are more susceptible to adverse reactions. So far, there have been no reports on supplement use by preschool children in Japan. Thus, a survey was conducted in the present study to clarify the factors and characteristics related to the use of supplements among the children in 7 prefectures.

The present research has several inherent limitations. The subjects of this study did not represent the population of the entire country; thus, the results cannot be applied to the Japanese population as a whole. All of our data were self-reported, leading to the possibility that the respondents may have misreported some data. Furthermore, the survey is cross-sectional and does not allow for causal inferences. Finally, because of constraints related to respondent burden, we were unable to collect information about the parent's education and income. However, to our knowledge, this is the first report to observe supplement use in preschool children in Japan, and the results provide important information about how we can face problems related to the use of supplements by children.

As Table 1 shows, the prevalence of supplement use was 15% among young children up to the age of 6 y, indicating that the supplement use among young Japanese children is not as prevalent as in the United States (17, 20, 22, 26–28). There are supplements that have been specially designed for children, but 69% of the parents of the supplement non-user children were unaware of the existence of such supplements. Therefore, the lack of awareness of children's supplements may be one reason for the low prevalence of children's supplement use in this survey. The supplement use by adults in the United States has been increasing (19, 29–31) and similar trends, although somewhat delayed, have been observed in Japan (7–9). The parents who were aware of the existence of children's supplements generally displayed an affirmative approach to children's supplement use. Such attitudes were evident in setting a low minimum age at which they started using supplements and in showing a strong likelihood to provide their children with supplements. Accordingly, it is expected that children's supplement use will expand in the future along with growing awareness of the existence of children's supplements, and use by babies and cases of addiction might be expected to occur as well.

In the present study, it was found that three factors are related to the promotion of supplement use by children (Table 1). These included the affiliation of the children (kindergartens versus day-care center), nutritional label use by parents, and parents' supplement use. In particular, parents who used supplements on a daily basis were 14 times more likely to give supplements to their children than the parents who did not use them. This observation coincided well with previous reports from the United States (20, 32, 33), indicating that the effect of the parents' history of supplement use is marked. These findings were expected because children

cannot decide about the use of supplements by themselves; therefore, children's supplement intakes are totally dependent on their parents' action.

Those parents who spent more time with their children (who attended kindergartens only for a short time) and those parents who referred to nutritional labels in selecting food were more likely to give their children supplements. These results are similar to the results of previous studies (32, 34), suggesting that the level of parents' interest towards nutritional balance, diet, and the welfare of their children relate to the use of supplements by their children. The parents' interest or sense of responsibility, rather than their pursuit of a way to take in nutrients, may lead to them supplying supplements to their children.

This questionnaire revealed two problems: the use of non-vitamin/mineral supplements and misunderstandings about the use of supplements by parents. Supplements should be used to supply ingredients that are in short supply in everyday meals. If the substances are vitamins and minerals, the evaluation of potential shortages can be made properly in general, because many of the nutrients have the adequate intake level and upper limit as the Dietary Reference Intakes (4) and are permitted to be labeled as Nutrient Function Claims (FNFC) by the Japanese government (3). On the other hand, the ingredients of non-Vitamin/Mineral often have poor evidence for their efficacy or safety and require particular care in their use. Thus, we divided the supplements into two categories (Vitamin/Mineral versus others ingredients) to analyze this survey. As a result, 32.5% of the child supplement users had experience in taking supplements that consisted of non-Vitamin/Mineral ingredients. The number of Non-Vitamin/Mineral users in Japan is slightly higher than in the United States, where about 80% of the child supplement users take supplements containing Vitamin/Minerals. It should be pointed out that some children also use herbal supplements (8.1%). Generally, the efficacy and safety of such herbs are not tested in children, and the intake of herbs by children may induce adverse reactions. In fact, attention has been drawn to the use of herbs both by adults and children because of safety issues (33, 35).

An excessive expectation and misunderstanding of dietary supplements by parents were suggested in this study. In purchasing supplements for children, parents confirmed the presence of nutritional labels and considered safety more seriously than efficacy, indicating that they have a strong desire to select safe products for their children. Nevertheless, these parents tended to select products with a natural source so as to avoid additives, while ignoring quality assurance guarantees such as the JHEA mark, which is an assurance of the quality of the products issued by the Japan Health Food and Nutrition Food Association. Consistent with a report in the United States (36), the use of supplements by Japanese children was based not on the advice of specialists but more frequently on consultation with friends and acquaintances. Furthermore, the parents who used the

non-Vitamins/Mineral supplements were characterized by their intention to promote health and prevent disease.

This phenomenon might be related to the flood of information available in the mass media. Mass media information is sometimes exaggerated, but is nevertheless perceived as truth by consumers, and therefore greatly influences supplement use and feeding behavior (37). In the present study, less than 20% of parents were aware of Dietary Reference Intakes (4), the dietary guidelines for Japanese, but considered the labels of foods that made nutrient claims related to the required amount and the health effects of certain vitamins and minerals for Japanese (3). These results show that parents cannot obtain proper knowledge about food and nutrition and the government systems related to nutritional labeling due to the poor communication system between consumers and professionals, and due to the flood of information released from the mass media.

The present findings indicate the existence of the same factors and characteristics related to the use of supplements among young children between Japan and the United States, although the culture, dietary habits, and governmental regulation systems are not the same. Some reports suggest that excessive nutrient intake or premature use of supplements is a health risk (22, 27), and other reports describe a lack of difference in nutrient intake from food between those children using and not using supplements (22, 32). In children who are still in the process of forming healthy dietary habits and are growing rapidly, reliance on supplements may result in a disregard for the importance of healthy daily eating habits. Easy use of supplements may be an obstacle for children to establishing a healthy diet in the future. Taken together, it is critical to give parents correct information relating to diet and nutrition, the importance of a balanced diet for children, and the food labeling system. With those individuals in mind, information on expanding the range of the study subjects with the characteristics of the daily or long term use and information on parents in relation to supplements and nutrition should be investigated in depth so that an appropriate response to supplement use can be formulated.

Acknowledgments

The authors express their gratitude to those who cooperated in this questionnaire. This study was supported by Health and Labour Sciences Research Grants (Research on Food Safety). The authors also thank those who assisted with the research.

REFERENCES

- Greger JL. 2001. Dietary supplement use: consumer characteristics and interests. *J Nutr* **131**: 1339S–1343S.
- Stanton C, Gardiner G, Meehan H, Collins K, Fitzgerald G, Lynch PB, Ross RP. 2001. Market potential for probiotics. *Am J Clin Nutr* **73**: 476S–483S.
- Yamada K, Sato-Mito N, Nagata J, Umegaki K. 2008. Health claim evidence requirements in Japan. *J Nutr* **138**: 1192S–1198S.
- Ministry of Health, Labour and Welfare of Japan. 2005. Dietary Reference Intakes for Japanese, 2005. Daiichi Syuppan, Tokyo (in Japanese).
- Ulbricht CE, Basch EM. 2005. Natural Standard Herb & Supplement Reference: Evidence-Based Clinical Reviews. Mosby Inc, St. Louis.
- Bent S. 2008. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J Gen Intern Med* **23**: 854–859.
- Ishihara J, Sobue T, Yamamoto S, Sasaki S, Akabane M, Tsugane S. 2001. Validity and reproducibility of a self-administered questionnaire to determine dietary supplement users among Japanese. *Eur J Clin Nutr* **55**: 360–365.
- Shi HJ, Nakamura K, Shimbo M, Takano T. 2005. Dietary supplement consumption among urban adults influenced by psychosocial stress: its pronounced influence upon persons with a less healthy lifestyle. *Br J Nutr* **94**: 407–414.
- Fukuda S, Watanabe E, Ono N, Tsubouchi M, Shirakawa T. 2006. Use of complementary and alternative medicine and health problems. *Nippon Koshu Eisei Zasshi* **53**: 293–300.
- Imai T, Nakamura M, Ando F, Shimokata H. 2006. Dietary supplement use by community-living population in Japan: data from the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). *J Epidemiol* **16**: 249–260.
- Ministry of Health, Labour and Welfare of Japan. 2003. The National Health and Nutrition Survey in Japan 2001. Daiichi Syuppan, Tokyo (in Japanese).
- Takahashi H, Kudo Y, Kanno K, Saito K, Ogasawara T, Matsumoto M, Yoshinaga K. 2000. A questionnaire study on health foods for cancer patients. *Jpn J Hosp Pharm* **26**: 95–101 (in Japanese).
- Itakura Y. 2005. Questionnaire survey of diet and diet-related foods by NCAC. *Shokuhin Eiseigaku Zasshi* **46**: J240–242 (in Japanese).
- Tanaka J, Konriki K, Raku M, Kawai K, Tokushima Y, Kubo K, Takasugi M. 2004. A questionnaire survey on patients' awareness regarding supplements. *J Jpn Soc Hosp Pharm* **40**: 37–39 (in Japanese).
- Ishihara J, Sobue T, Yamamoto S, Sasaki S, Tsugane S. 2003. Demographics, lifestyles, health characteristics, and dietary intake among dietary supplement users in Japan. *Int J Epidemiol* **32**: 546–553.
- Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. 1998. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* **280**: 1569–1575.
- Balluz LS, Kieszak SM, Philen RM, Mulinare J. 2000. Vitamin and mineral supplement use in the United States. Results from the third National Health and Nutrition Examination Survey. *Arch Fam Med* **9**: 258–262.
- Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altman DE. 2001. Americans' views on the use and regulation of dietary supplements. *Arch Intern Med* **161**: 805–810.
- Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. 2004. Dietary supplement use by US adults: data from the National Health and Nutrition

- Examination Survey, 1999–2000. *Am J Epidemiol* **160**: 339–349.
- 20) Eichenberger Gilmore JM, Hong L, Broffitt B, Levy SM. 2005. Longitudinal patterns of vitamin and mineral supplement use in young white children. *J Am Diet Assoc* **105**: 763–772; quiz 773–764.
 - 21) Timbo BB, Ross MP, McCarthy PV, Lin CF. 2006. Dietary supplements in a national survey: Prevalence of use and reports of adverse events. *J Am Diet Assoc* **106**: 1966–1974.
 - 22) Briefel R, Hanson C, Fox MK, Novak T, Ziegler P. 2006. Feeding infants and toddlers study: do vitamin and mineral supplements contribute to nutrient adequacy or excess among US infants and toddlers? *J Am Diet Assoc* **106**: S52–65.
 - 23) Rock CL. 2007. Multivitamin-multimineral supplements: who uses them? *Am J Clin Nutr* **85**: 277S–279S.
 - 24) Ministry of Health, Labour and Welfare of Japan. 2006. *The National Health and Nutrition Survey in Japan, 2004*. Daiichi Syuppan, Tokyo (in Japanese).
 - 25) Ministry of Health, Labour and Welfare of Japan/Ministry of Agriculture, Forestry and Fisheries of Japan. 2005. *Japanese Food Guide Spinning Top*. Daiichi Syuppan, Tokyo (in Japanese).
 - 26) Yu SM, Kogan MD, Gergen P. 1997. Vitamin-mineral supplement use among preschool children in the United States. *Pediatrics* **100**: E4.
 - 27) Milner JD, Stein DM, McCarter R, Moon RY. 2004. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. *Pediatrics* **114**: 27–32.
 - 28) Picciano MF, Dwyer JT, Radimer KL, Wilson DH, Fisher KD, Thomas PR, Yelley EA, Moshfegh AJ, Levy PS, Nielsen SJ, Marriott BM. 2007. Dietary supplement use among infants, children, and adolescents in the United States, 1999–2002. *Arch Pediatr Adolesc Med* **161**: 978–985.
 - 29) Block G, Cox C, Madans J, Schreiber GB, Licitra L, Melia N. 1988. Vitamin supplement use, by demographic characteristics. *Am J Epidemiol* **127**: 297–309.
 - 30) Koplan JP, Annett JL, Layde PM, Rubin GL. 1986. Nutrient intake and supplementation in the United States (NHANES II). *Am J Public Health* **76**: 287–289.
 - 31) Ervin RB, Wright JD, Kennedy-Stephenson J. 1999. Use of dietary supplements in the United States, 1988–94. *Vital Health Stat* **11** **244**: i–iii, 1–14.
 - 32) Lee Y, Mitchell DC, Smiciklas-Wright H, Birch LL. 2002. Maternal influences on 5- to 7-year-old girls' intake of multivitamin-mineral supplements. *Pediatrics* **109**: E46.
 - 33) Lohse B, Stotts JL, Priebe JR. 2006. Survey of herbal use by Kansas and Wisconsin WIC participants reveals moderate, appropriate use and identifies herbal education needs. *J Am Diet Assoc* **106**: 227–237.
 - 34) Kurakami H, Wakamatsu H. 2003. Study on ingestion of food by children regarding guardian's concern with nutrition balance. *Health Sciences* **19**: 112–121 (in Japanese).
 - 35) Bardia A, Nisly NL, Zimmerman MB, Gryzlak BM, Wallace RB. 2007. Use of herbs among adults based on evidence-based indications: findings from the National Health Interview Survey. *Mayo Clin Proc* **82**: 561–566.
 - 36) Lanski SL, Greenwald M, Perkins A, Simon HK. 2003. Herbal therapy use in a pediatric emergency department population: expect the unexpected. *Pediatrics* **111**: 981–985.
 - 37) Cyranoski D. 2007. Japanese TV show admits faking science. *Nature* **445**: 804–805.



Question

ダイエット関連健康食品の有害事象は？

ダイエット関連健康食品の有害事象について教えてください。

山田 浩¹⁾，山田 薫²⁾

¹⁾ 静岡県立大学薬学部医薬品情報解析学，²⁾ 聖隷予防検診センター

Answer

ダイエット関連健康食品は昨今、非常に多く市場に出回り、海外で販売されているものもインターネットなどを介して一般の消費者が容易に入手できる状況にあります。それら健康食品の多くは有効性のエビデンスが明らかでないままに、痩身効果の期待から消費者が安易に摂取し、それによる有害事象が後を絶たないことが社会的に大きな問題となっています。

ダイエット関連健康食品の有害事象が発生する原因には、医薬品成分の違法添加、食品として日常摂取する以上の過剰摂取、個々の体質の違いによる過敏反応、併用医薬品や食品との相互作用によるものなどがあります(表)。有害事象の発生原因を科学的に吟味することは、的確な治療や発生の予防につながり、大変重要です。以下、今まで社会的に大きな問題となったダイエット関連健康食品の有害事象を紹介していきます¹⁾。

2002年に日本国内で、中国製ダイエット関連健康食品を摂取した女性が重篤な肝障害で死亡した事例が報告されました。その後、同様の肝障害の報告が国内で600例を超え、3名の死亡例を出すに至っています。肝障害を来した健康食品からは、食欲抑制剤、甲状腺素、緩下剤、利尿剤などの医薬品が検出されています(表)。最近では、日本で認可されていない肥満抑制薬のシブトラミンが使用されたことによる死亡例が報告されています。シブトラミンは、

中国製および韓国製のダイエット関連健康食品に含まれていることが多く、海外からの輸入による摂取に注意が必要です。シブトラミンの主な副作用は、不眠、頭痛、吐き気、口内乾燥、便秘などがあり、重篤な心血管系の副作用として血圧および心拍数の増加、不整脈があります²⁾。医薬品との相互作用として、うつ病あるいはパーキンソン病の治療薬である選択的セロトニン再取り込み阻害薬やモノアミン酸化酵素阻害薬の併用により副作用が増す可能性があるため、併用時には注意が必要です。

過剰摂取や過敏反応によるダイエット関連の有害事象として、エフェドラとアマメシバの事例が挙げられます。エフェドラは、米国食品医薬品局(FDA)が栄養補助食品を販売禁止とした最初の健康食品です。2003年、エフェドラ含有の栄養補助食品を常用していた米国大リーグ投手が、トレーニング中に突然死しました。米国では、その後もエフェドラによる心血管系の副作用による死亡例が続出し、2004年にFDAは販売を禁止しました。エフェドラは、漢方薬「麻黄」由来のエフェドリンが主成分であり、交感神経興奮作用を有し、代謝促進や覚醒の働きがある一方、動悸、高血圧などの心血管系および精神異常などの中枢神経系の副作用があり、重症になると心筋梗塞や致死的不整脈を来します³⁾。日本においても、エフェドラとカフェインを含むサプリメントを大量摂取し、重症の

表 有害事象の発生原因と具体的なダイエット関連健康食品例

発生原因	ダイエット関連健康食品例
医療の違法添加	<ul style="list-style-type: none"> ・食欲抑制剤 (N-ニトロソフェンフルラミン, フェンフルミラン, マジンドール, シブトラミン) ・甲状腺末 ・緩下剤 (センノシド) ・利尿薬 (ヒドロクロロチアジド, フロセミド) ・麻黄 (エフェドリン) など
過剰摂取	<ul style="list-style-type: none"> ・エフェドラ ・アマメシバなど
過敏反応 (皮膚皮膚病変やアナフィラキシーなど)	<ul style="list-style-type: none"> ・アマメシバなど
併用医薬品や食品との相互作用	<ul style="list-style-type: none"> ・エフェドラとカフェイン (強壮剤やハーブティーとの混入) など

心室細動を起こした事例が報告されています。

アマメシバは、日本における食品衛生法に基づき販売禁止となった健康食品の第1号です。アマメシバの摂取による有害事象は、1996年から台湾各地で閉塞性細気管支炎の事例が多数報告されました。日本では、2003年にアマメシバの摂取による閉塞性細気管支炎の初発例が報告されています。その後の全国調査による8事例の集計によると、主な症状は進行性の呼吸困難と咳であり、肺障害の多くは不可逆的で治療に対する反応性は乏しく、呼吸不全により死に至ったり、肺移植手術や在宅酸素療法を要する事例が示されています⁴⁾。発生の原因としては、アマメシバを生鮮未調理で濃縮して加工後、継続的に大量に摂取したことや、個人の免疫応答における感受性の違いなどが推定されています。

エフェドラやアマメシバが販売禁止となったとはいえ、その成分がハーブティーの中に混在

したり、インターネットオークションなどを介して消費者が海外から個人輸入して使用する可能性は依然としてあります。ダイエット関連健康食品の有害事象を未然に防ぐためには、“痩せたいために”という理由で消費者が安易に健康食品を使用しない様に働きかけることが非常に重要です。

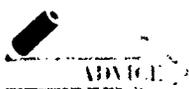
文 献

- 1) 山田 浩：健康食品の有害事象の事例と解説 ③ダイエット関連事例, *Functional Food* 2(1) : 96-99, 2008
- 2) Wooltorton E : Obesity drug sibutramine (Meridia) : hypertension and cardiac arrhythmias. *CMAJ* 166(10) : 1307-1308, 2002
- 3) Haller CA, Benowitz NL : Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 343(25) : 1833-1838, 2000
- 4) 東元一見, 大中原研一, 松山航, ほか : 薬剤性肺疾患 診断と治療の進歩 ; 主な薬剤性肺障害 サプリメント, 日内会誌 96(6) : 1149-1155, 2007

KEY WORDS

シブトラミン：シブトラミンは、1997年に米国FDAが認可した肥満抑制薬であり、日本では市販前の治験段階です。脳内神経伝達物質のセロトニンおよびノルアドレナリンなどモノアミンの再取り込みを阻害することにより満腹感を亢進し、食欲抑制をもたらすと共に、エネルギー消費を促進させる作用を併せ持っています。

閉塞性細気管支炎：細気管支に病変の主座を有し、閉塞性換気障害を来す治療抵抗性の呼吸器疾患です。検査では、低酸素血症と肺機能検査における著明な1秒量の低下を認め、呼気時胸部CT検査では特徴的な低吸収域のモザイクパターンを示します。



ADVICE

・ダイエットの基本は、健康的なバランスの取れた食事と適度の運動、そして暴飲暴食などの不健康な生活行動を正すことであり、決してダイエット関連健康食品で安易に達成できるものではないことを、医療従事者は、消費者に強調して、し過ぎることはありません。

・ダイエット関連健康食品は強壮剤やハーブティーとの複合健康食品として販売されることも多く、その場合には含有されるカフェインなどの過剰摂取や相互作用にも注意を払う必要があります。

健康食品摂取と健康上の有害事象の因果関係を評価するためのアルゴリズムの提案

山田 浩^{*1} 松本 圭司^{*1,2} 清水 雅之^{*1}
 熊谷 翼^{*1} 渡邊 崇之^{*1} 近都 正幸^{*1}
 朴 美貞^{*1} 小菅 和仁^{*1} 川上 純一^{*2}
 梅垣 敬三^{*3}

Study on Modified Algorithms for the Evaluation of Causal Relationships of Adverse Events with Health Food Products or Supplement Consumption

Hiroshi YAMADA^{*1} Keiji MATSUMOTO^{*1,2} Masayuki SHIMIZU^{*1}
 Tasuku KUMAGAI^{*1} Takayuki WATANABE^{*1} Masayuki KINTSU^{*1}
 Mijong PARK^{*1} Kazuhiro KOSUGE^{*1} Junichi KAWAKAMI^{*2}
 and Keizo UMEGAKI^{*3}

^{*1} Division of Drug Evaluation & Informatics, School of Pharmaceutical Sciences, University of Shizuoka
 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

^{*2} Hamamatsu University School of Medicine

^{*3} National Institute of Health and Nutrition

Health food products or supplements are expected to promote health and to prevent and treat diseases ; consequently their use has recently increased. Therefore, it is necessary to accurately and efficiently examine adverse events associated with them. Many algorithms for the evaluation and classification of causal relationships of adverse events related to medications have been proposed, however, there is no algorithm concerning health food products or supplements. In this study, considering these circumstances, we designed algorithms for the evaluation and classification of causal relationships of adverse events with health food products or supplements and evaluated their reliability. The algorithms previously proposed for the evaluation and classification of causal relationships of adverse events with medication (Naranjo CA, *et al.* Clin Pharmacol Ther 1981 ; 30 : 239-45, Jones JK. Fam Community Health 1982 ; 5 : 58-67) were modified for the present study. We assessed the effects of the ginkgo biloba extract, a common health food supplement, and reviewed the literature using databases such as MEDLINE. We found 29 cases of adverse events related to intake of ginkgo biloba extracts. Using the modified algorithms, the causal relationship of ginkgo biloba extracts with adverse events in the cases was independently evaluated by 4 raters (a clinician and 3 pharmacists), and the inter-rater reliability was tested. The coefficient of intra-class correlation calculated by the total score of Naranjo *et al.* was 0.65 and the 95% confidence interval was [0.48, 0.79]. The κ coefficient of multi-rater reliability was 0.27 in the algorithm of Naranjo *et al.*, while it was, 0.26 when 5 studies were excluded using the algorithm of Jones. In conclusion, the modified algorithm of Naranjo *et al.* may be recommended for evaluating causal relationships of adverse events with health food products or supplement consumption.

Key words : health food, supplements, algorithm, adverse effects, ginkgo biloba

^{*1} 静岡県立大学薬学部医薬品情報解析学分野 ^{*2} 浜松医科大学医学部附属病院薬剤部 ^{*3} 独立行政法人国立健康・栄養研究所情報センター

別刷請求先：山田浩 静岡県立大学薬学部医薬品情報解析学分野 〒422-8526 静岡市駿河区谷田52-1

(投稿受付2008年11月13日, 第2稿受付2009年2月26日, 第3稿受付2009年3月31日, 第4稿受付2009年4月9日, 掲載決定2009年4月15日)

緒 論

近年、消費者の健康志向の高まりを受け、サプリメント等の栄養補助食品や、いわゆる健康食品等（以下、両者を総称して健康食品と略す）が、店頭やインターネット等を介して一般の消費者が容易に入手できる状況となった。その一方で、消費者がテレビやインターネット等で発信される不確かな情報を基に健康食品を摂取している現状がみられ、健康食品が原因と疑われる健康被害事例が問題となっている¹⁻³⁾。

健康食品の摂取に伴う有害事象が発生した場合、その健康食品が原因と判断するためには、報告された有害事象情報についての正確な評価が必要となる。しかし現在のところ、医療現場から報告される健康食品の摂取に伴う有害事象報告は種々雑多であり、因果関係について科学的に十分吟味された情報として社会に還元されているとは言い難い。また、その情報を臨床現場において正確かつ効率的に判定する評価法も僅かしか提案されていない⁴⁾。

すでに医薬品においては、有害事象の因果関係の評価として、評価票あるいは樹枝状の選択肢を用いた種々のアルゴリズムが考案されている⁵⁻⁹⁾。健康食品の摂取に伴う有害事象の因果関係の評価を考える場合、医薬品と同じような薬理作用を示す成分を含むもの、用量依存性に反応が生じるもの、薬物代謝酵素に影響を与えるものなどが存在し、基本的には医薬品同様の薬理作用や薬力学的なアプローチが必要となることから、健康食品の有害事象にもこれらのアルゴリズムでの評価が可能と考えられる。そこで今回、医薬品の有害事象の評価で比較的良好に使われている、Naranjo らアルゴリズム⁵⁾と、Jones アルゴリズム⁶⁾を基に、健康食品を対象とした評価アルゴリズムを設計し、その信頼性評価を行うこととした。

方 法

医薬品の有害事象における因果関係の評価分類アルゴリズムとして使用頻度が高い Naranjo らおよび Jones アルゴリズムを、健康食品用に改変したもの（以下それぞれ、Naranjo ら改変アルゴリズム、Jones 改変アルゴリズムと略す）を設計した (Table 1, Fig)。具体的には、それぞれのアルゴリズムを和訳し、“医薬品”という単語を“健康食品”に置き換え、それにより生じる文章的に不適切な表現を修正した。両アルゴリズムの各質問項目の内容や、Naranjo らアルゴリズムの点数の重み付けおよび Total score に基づく判定

基準については、オリジナルのアルゴリズムのまま変更を加えなかった。

今回、評価の対象とした健康食品は、世界で最も利用が多い健康食品の1つであるイチョウ葉エキス (Ginkgo biloba extract) とし、その摂取に伴う有害事象に関する臨床文献を網羅的に収集した。二次文献として MEDLINE、医学中央雑誌を利用し、検索可能な年代から 2007 年 6 月までに登録されている英語および和文献を検索した。検索語には、MEDLINE では MeSH term として ginkgo biloba と adverse effects または hypersensitivity を選び、医学中央雑誌ではイチョウ葉エキスと副作用または相互作用を選んだ。さらに、三次文献として独立行政法人国立健康・栄養研究所ホームページを利用し、そこで引用されている文献についても同様に対象として収集した。収集した文献のアルゴリズムの適用に関しては、イチョウ葉エキスの摂取に伴う有害事象に関する症例報告の記述があり、英語か日本語で書かれた文献を評価の対象として採用した。

評価者は1人の医師（日本臨床薬理学会認定医）と3人の薬剤師（薬剤師免許を有する修士大学院生）とした。各文献は、今回作成した2つのアルゴリズムを利用して、各評価者により独立して有害事象の因果関係の評価を行った。各評価者が評価する文献の順番は単純ランダム化した。

評価された結果の解析においては、評価者により一部でも記入のあったすべての評価アルゴリズムを解析対象とした。また評価者の属性（医師、薬剤師）による評価傾向の相違を検討するため医師を除いた薬剤師のみの解析を行った。評価者間信頼性の解析は、Naranjo ら改変アルゴリズムでは Total score を対象として、有害事象例間の変動と評価者間の変動を変量効果とみなした二元配置分散分析モデルを当てはめ、評価者間信頼性係数とその 95% 信頼区間を推定した。また、Naranjo ら改変アルゴリズムの Total score に基づく分類結果（4段階）、Jones 改変アルゴリズムの分類結果（4段階）に関しては、観測一致率と、Schouten による多評価者間 κ 係数、さらに一次・二次重み付き κ 係数をそれぞれ推定した¹⁰⁾。

結 果

対象として抽出した有害事象は 29 例（抽出文献として英語文献 26 件、和文献 1 件）であった (Table 2)。具体的な有害事象は、出血傾向（前房出血、大脳出血、硝子体出血等）が 17 件、てんかん発作の誘発が 3 件、