Our study also had several limitations. First, we used only baseline information on green tea consumption, and thus could not assess the effects of lifetime consumption on risk or changes in consumption during follow-up. Non-consumers of green tea are rare in Japan and it is possible that these subjects are a selection of the population that is at increased risk of gastric cancer. Some subjects with gastric cancer might have decreased their consumption before the diagnosis because of their symptoms. Likewise, it is possible that the observed protective effect of green tea among heavy drinkers only might be that the gastrointestinal symptoms associated with *H pylori* infection might force a person to avoid drinking green tea. Such change in practice might have biased their recall of past intake in such a way that they underestimated their true consumption, resulting in spurious inverse association. However, analyses of each cohort which excluded the early cases did not substantially change the results.[9 10 13 14] Second, the proportion of missing values for green tea consumption among the study subjects was 4.2% and excluded from the study. The exclusion of these subjects may have distorted the results, although the proportion was low and any influence may not have been substantial. Third, random variation related to exposure measurement might have attenuated the associations. In addition, we used the indicator terms for missing covariates, and this may have introduced bias. The proportion of missing data was 8.6% for smoking, 8.1% for alcohol intake, 2.7% for rice intake, 2.2% for soy bean paste soup intake, 15.7% for coffee intake, 4.1% for pickled vegetable intake and 4.5% green–yellow vegetable intake, showing variation by covariate, some cases of which were not negligible. We conducted analyses which were restricted to subjects with complete information and obtained closely similar values. Fourth, we are unable to exclude the possibility that our estimates were distorted because of residual confounding. Finally, we did not obtain information on *H pylori* infection status for the whole population, a strong risk factor for gastric cancer. Green tea is suggested to have antibacterial effects,[37–39] and green tea may be associated with gastric cancer risk through the effect of green tea on this infection. It is therefore likely that the failure to adjust for this infection may have resulted in the apparent protective effect of green tea on gastric cancer risk.

Allowing for these methodological issues, this pooled analysis of data from large prospective studies in Japan confirmed a significant decrease in risk of gastric cancer among women with high green tea consumption, especially for the distal subsite. Further investigation of our findings of differences in effect by sex and subsite will help elucidate the mechanism underlying the etiology of gastric cancer.

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# Editor's quiz: GI snapshot

Robin Spiller, *editor*

## Epigastric pain in a man with previous subtotal gastrectomy

### CLINICAL PRESENTATION

A 68-year-old man presented to our hospital with a 2-day history of upper abdominal pain and non-bilious vomiting. Twenty years previously he had undergone a subtotal gastrectomy with Billroth II reconstruction because of a gastric ulcer. He denied alcohol consumption or trauma. Physical examination revealed that his upper abdomen was tender with muscle guarding and rebound tenderness. Laboratory tests showed the following: haemoglobin 11 g/dl (normal, 14–16 g/dl), white blood count $12.9\times10^9$/l (normal, $4.0–10.0\times10^9$/l), amylase 1744 IU/l (normal, 27–131 IU/l) and lipase 4587 IU/l (normal, 8–58 IU/l). Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline (fig 1). Additionally, a 5×3 cm lesion was identified on CT images showing the target sign in the proximal segment of the afferent loop (fig 2). A diagnosis of afferent loop syndrome (ALS) complicated by acute pancreatitis was made based on symptoms, laboratory studies and CT images. The patient underwent an emergency laparotomy.

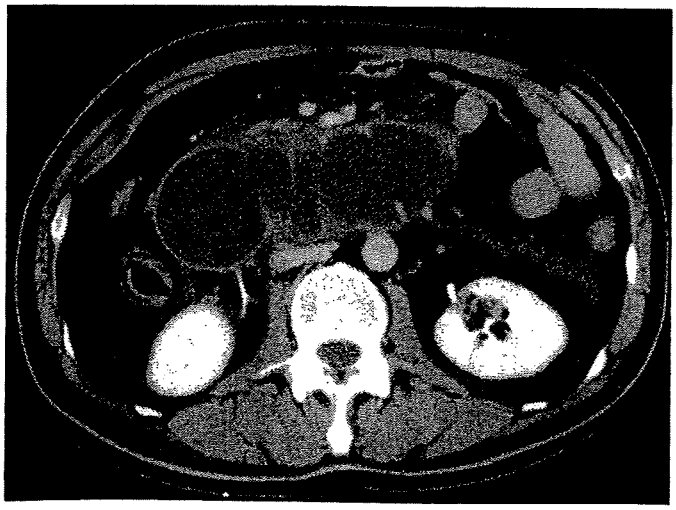

**Figure 1** Abdominal CT scan demonstrated a markedly distended, fluid-filled afferent loop crossing the midline.

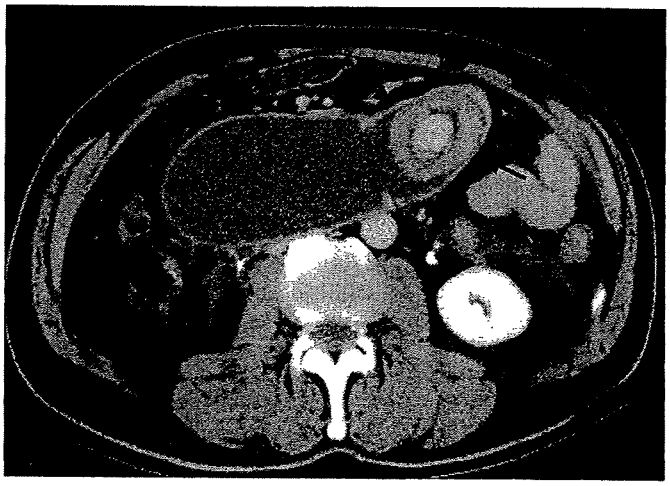

**Figure 2** A 5×3 cm lesion with target sign in the proximal segment of afferent loop was identified on CT images (arrows).

### QUESTION

What is the cause of afferent loop syndrome?

*See page 1436 for the answer.*

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## *Short Communication*

# Association of intakes of fat, dietary fibre, soya isoflavones and alcohol with uterine fibroids in Japanese women

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Certain dietary components which could affect oestrogen may have implications in the aetiology of uterine fibroids. We previously found that soya intake was inversely associated with a subsequent risk of hysterectomy, suggesting a potentially protective effect of soya against uterine fibroids, the major clinical indication for hysterectomy. We cross-sectionally assessed the associations of intakes of fat, soya foods, dietary fibre and alcohol with uterine fibroids. Study subjects were 285 premenopausal Japanese women participating in a health-check up programme, including gynaecological examinations, provided by a general hospital between October 2003 and March 2006. The presence of fibroids was confirmed by transvaginal sonogram. If women had undergone hysterectomy, self-report of fibroids was accepted. Each subject's usual diet, including alcohol, was determined with the use of a validated FFQ. Fifty-four women were identified as prevalent cases of fibroids or having had hysterectomy due to fibroids. The mean alcohol intake was statistically significantly higher among women with fibroids than among those without fibroids after controlling for known or suspected risk factors. For the highest compared with the lowest tertile of alcohol intake, the OR of uterine fibroids was 2·78 (95 % CI 1·25, 6·20). There was no significant association of intake of fats, soya isoflavones or dietary fibre with uterine fibroids. The data suggest that higher alcohol intake is associated with a higher prevalence of uterine fibroids. Further studies on diet, especially phyto-oestrogens, and uterine fibroids are needed given the limited data currently available.

**Uterine fibroids: Alcohol: Soya: Diet**

Uterine fibroids are the most common tumours among women of reproductive age[1]. Although the mechanisms are not well understood, clinical and laboratory evidence indicates that oestrogen and progesterone may both be important promoters of myoma growth[2]. Certain dietary components which could affect oestrogen or progesterone may be implicated in the aetiology of fibroids. Dietary fat, soya foods, dietary fibre and alcohol have been associated with endogenous oestrogen levels in some studies[3–5]. Previous studies have assessed the association of fibroids with alcohol intake[6–8]. However, to our knowledge, only two studies have assessed the relationship between dietary intake other than alcohol and uterine fibroids[6,9]. In a study reported by Chiaffarino *et al.* [6], the consumption of beef and other red meats was positively associated with the risk of fibroids. However, no attempt was made to estimate quantitatively the intake of individual nutrients such as fat. Another study focused on dietary carotenoids in relation to the risk of uterine fibroids and observed no risk reduction[9]. Both studies did not investigate the relationship between soya intake and fibroids. We previously found that soya intake was inversely associated with the risk of hysterectomy in a population-based cohort study of Japanese women[10], suggesting a potentially protective effect of soya against uterine fibroids, the major clinical indication for hysterectomy. In a recent case–control study of fibroids among US women, Atkinson *et al.* [11] observed that urinary excretion of lignan, a phyto-oestrogen, was significantly lower among cases than that among controls. They found no significant difference in urinary isoflavone excretion between cases and controls. However, they noted that the intake of soya foods, the primary source of isoflavones, was apparently low in the study population. Excretion of lignans and isoflavones is a short-term biomarker that may be unsuitable to capture a long-term exposure, which is the exposure of interest when chronic diseases are investigated. In the present cross-sectional study, we examined the association between uterine fibroids and diet, including fats, soya isoflavones, dietary fibre and alcohol, among Japanese women.

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## Methods

The present study was part of one designed to assess the relationships among lifestyle, environmental factors and women's health. Study subjects were participants in a medical health check-up programme provided by a general hospital in Gifu, Japan, between October 2003 and March 2006. The purpose of the medical health check-up is to promote public health through early detection of chronic diseases and their risk factors. A medical service of this kind is popular in Japan. A total of 2073 individuals, including return visitors to the programme during the study period, were invited to join the study, and 1545 agreed to participate (the response proportion was 74·5 %). When the response proportion was calculated for only new visitors to the programme during the study period, it was 83·2 % (1103 out of 1325 individuals).

The participants responded to a self-administered questionnaire that included questions on demographic characteristics, smoking and drinking habits, diet, exercise, and medical and reproductive histories. Diet including alcohol intake was assessed with a validated 169-item semi-quantitative FFQ. The participants were asked how often on average they consumed each of the food items listed and what was the usual serving size of each item during the year before the study. Intakes of foods and nutrients were estimated from the frequency of ingestion and portion size using the Japanese Standard Tables of Food Composition, 4th and 5th editions, published by the Science and Technology Agency of Japan. The questions on alcohol use included six different types of liquor, which were sake, beer, light beer, shochu (distilled from sweet potatoes, rice or buckwheat), wine and hard liquor. For each item, the questionnaire included seven frequency categories (from never/less than once per month to once per d or more) and the number of cups, glasses and bottles consumed. Detailed information on the questionnaire including its validity and reproducibility examined in other samples has been described elsewhere[12,13]. For example, the Spearman correlation coefficients between the questionnaire and twelve daily diet records kept over a 1-year period for intakes of total energy, macronutrients, dietary fibre, soya isoflavones and alcohol ranged from 0·45 to 0·64. Our questionnaire was designed to measure an individual's relative intakes of foods and nutrients rather than absolute values. The means estimated from the FFQ were generally higher than those estimated from twelve daily diet records. Although we presented the mean values of dietary intake, some of them may have been overestimated by our questionnaire.

The present study was limited to female subjects undergoing gynaecological examinations including a Pap smear test, pelvic examination and transvaginal ultrasound screening. A total of 539 women underwent these examinations. As fibroids can shrink after menopause, 122 postmenopausal women were excluded from the study. Women who had been without a menstrual cycle in the past 12 months were classified as postmenopausal. The presence of fibroids was assessed by transvaginal sonogram. Only fibroids with a diameter of 10 mm or more were registered. The size of the largest fibroid was conventionally classified into seven categories (from thumb-size to infant head-size). If a woman had undergone a hysterectomy, self-report of fibroids was accepted. Women who had not responded to the dietary questionnaire (*n* 108) or those with incomplete or unreliable responses to the dietary questionnaire (criteria shown elsewhere[14], for example, staple food five times per d or more) (*n* 19) were excluded from the present analyses. Additionally, five women who had cancer were excluded. Thus, 285 premenopausal women aged 23–56 years comprised the study population. Informed consent was obtained from each subject. The present study was approved by the ethical board of the Gifu University Graduate School of Medicine.

For statistical analysis, dietary intakes were adjusted for total energy after log-transformation by using the residual method proposed by Willett[15]. Alcohol intake was also log-transformed. OR and 95 % CI of uterine fibroids were computed according to the tertile of energy-adjusted dietary intakes using the unconditional logistic regression model. The linear trends were assessed using continuous values of the dietary variables. The known or suspected risk factors for fibroids, such as age, parity, BMI, smoking status and age at menarche were included in the models as covariates. Some symptoms related to fibroids may make women change their diet. Therefore, we repeated analyses after excluding women who had reported cramps or abnormal bleeding. All the statistical analyses were performed using SAS programs (SAS Institute, Inc., Cary, NC,

**Table 1.** Characteristics of study subjects according to uterine fibroid status

| | With fibroids (*n* 54) | | Without fibroids (*n* 231) | |
|---|---|---|---|---|
| Variables | *n* | % | *n* | % |
| Age (years) | | | | |
| < 35 | 2 | 3·7 | 35 | 15·2 |
| 35–39 | 14 | 25·9 | 56 | 24·2 |
| 40–44 | 13 | 24·1 | 71 | 30·7 |
| 45–49 | 19 | 35·2 | 51 | 22·1 |
| 50 + | 6 | 11·1 | 18 | 7·8 |
| BMI (kg/m$^2$) | | | | |
| < 19·0 | 10 | 18·5 | 44 | 19·0 |
| 19·1–20·9 | 19 | 35·2 | 79 | 34·2 |
| 21·0–23·9 | 14 | 25·9 | 75 | 32·5 |
| 24 + | 11 | 20·4 | 33 | 14·3 |
| Age at menarche (years) | | | | |
| < 13 | 22 | 40·7 | 93 | 40·3 |
| 13 | 18 | 33·3 | 12 | 22·2 |
| 14 + | 12 | 22·2 | 67 | 29·0 |
| Unknown | 2 | 3·7 | 14 | 6·1 |
| Number of live births | | | | |
| 0 | 17 | 31·5 | 30 | 13·0 |
| 1–2 | 31 | 57·4 | 130 | 56·3 |
| 3 + | 4 | 7·4 | 60 | 26·0 |
| Unknown | 2 | 3·7 | 11 | 4·8 |
| Age at first birth (years)* | | | | |
| < 25 | 11 | 31·4 | 52 | 27·4 |
| 25–26 | 11 | 31·4 | 72 | 37·9 |
| 27 + | 13 | 37·1 | 66 | 34·7 |
| Age at last birth (years)* | | | | |
| < 28 | 15 | 42·8 | 46 | 24·2 |
| 28–30 | 7 | 20·0 | 66 | 34·7 |
| 31 + | 12 | 34·3 | 73 | 38·4 |
| Unknown | 1 | 2·9 | 5 | 2·6 |
| Smoking status | | | | |
| Never smokers | 47 | 87·0 | 213 | 92·2 |
| Current smokers | 6 | 11·1 | 10 | 4·3 |
| Ex-smokers | 1 | 1·9 | 8 | 3·5 |
| Current HRT use | 1 | 1·9 | 7 | 3·0 |
| Current OC use | 1 | 1·9 | 2 | 0·9 |

HRT, hormone replacement therapy; OC, oral contraceptive.
* Among parous women.

**Table 2.** Risk of prevalent fibroids by tertile of selected dietary factors
(Odds ratios and 95 % confidence intervals)

| Variables | Median* | Prevalence | OR† | 95 % CI | OR‡ | 95 % CI |
|---|---|---|---|---|---|---|
| Total energy (kJ/d) | | | | | | |
| Low | 6502 | 21/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 8586 | 18/95 | 0·78 | 0·39, 1·61 | 0·80 | 0·37, 1·73 |
| High | 11 011 | 15/95 | 0·66 | 0·31, 1·38 | 0·75 | 0·34, 1·68 |
| *P* for trend | | | 0·90 | | 0·74 | |
| Total fat (g/d) | | | | | | |
| Low | 54·1 | 17/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 62·8 | 23/95 | 1·56 | 0·78, 3·16 | 1·65 | 0·77, 3·57 |
| High | 71·0 | 14/95 | 0·78 | 0·35, 1·71 | 1·22 | 0·52, 2·86 |
| *P* for trend | | | 0·82 | | 0·56 | |
| SFA (g/d) | | | | | | |
| Low | 14·6 | 19/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 18·3 | 16/95 | 0·85 | 0·40, 1·78 | 1·03 | 0·47, 2·29 |
| High | 21·8 | 19/95 | 1·10 | 0·53, 2·26 | 1·22 | 0·56, 2·65 |
| *P* for trend | | | 0·54 | | 0·87 | |
| MUFA (g/d) | | | | | | |
| Low | 18·2 | 16/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 21·4 | 24/95 | 1·72 | 0·84, 3·50 | 2·00 | 0·90, 4·42 |
| High | 25·0 | 14/95 | 0·95 | 0·43, 2·10 | 1·37 | 0·57, 3·29 |
| *P* for trend | | | 0·67 | | 0·57 | |
| PUFA (g/d) | | | | | | |
| Low | 13·0 | 15/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 15·3 | 20/95 | 1·36 | 0·65, 2·90 | 1·61 | 0·71, 3·65 |
| High | 18·1 | 19/95 | 1·29 | 0·61, 2·76 | 1·87 | 0·80, 4·37 |
| *P* for trend | | | 0·46 | | 0·14 | |
| Dietary fibre (g/d) | | | | | | |
| Low | 11·9 | 16/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 14·7 | 15/95 | 0·98 | 0·46, 2·10 | 0·89 | 0·39, 2·04 |
| High | 19·5 | 23/95 | 1·36 | 0·65, 2·82 | 1·44 | 0·66, 3·17 |
| *P* for trend | | | 0·42 | | 0·55 | |
| Soya isoflavones (mg/d) | | | | | | |
| Low | 21·2 | 13/95 | 1·00 | Reference | 1·00 | Reference |
| Middle | 35·4 | 20/95 | 1·66 | 0·77, 3·58 | 2·02 | 0·88, 4·66 |
| High | 61·1 | 21/95 | 1·67 | 0·78, 3·60 | 1·82 | 0·79, 4·17 |
| *P* for trend | | | 0·27 | | 0·26 | |
| Total alcohol (g/d) | | | | | | |
| Low | 0 | 14/103 | 1·00 | Reference | 1·00 | Reference |
| Middle | 0·9 | 14/87 | 1·32 | 0·59, 2·97 | 1·37 | 0·57, 3·25 |
| High | 9·0 | 26/95 | 2·62 | 1·26, 5·44 | 2·78 | 1·25, 6·20 |
| *P* for trend | | | 0·0004 | | 0·001 | |
| Beer and light beer | | | | | | |
| Low | 0 | 20/103 | 1·00 | Reference | 1·00 | Reference |
| Middle | 0·5 | 8/60 | 0·89 | 0·37, 2·17 | 0·94 | 0·37, 2·40 |
| High | 4·0 | 26/92 | 2·32 | 1·20, 4·51 | 2·75 | 1·30, 5·83 |
| *P* for trend | | | 0·0008 | | 0·001 | |
| Other types of liquor | | | | | | |
| Low | 0 | 23/159 | 1·00 | Reference | 1·00 | Reference |
| Middle | 0·4 | 6/33 | 1·38 | 0·51, 3·74 | 1·40 | 0·49, 4·04 |
| High | 3·4 | 25/95 | 2·34 | 1·23, 4·46 | 1·79 | 0·88, 3·62 |
| *P* for trend | | | 0·01 | | 0·07 | |

* Adjusted for total energy except for total energy and alcohol intake.
† Age-adjusted.
‡ Adjusted for age (continuous), BMI (continuous), smoking status (never, ex- and current smokers), no. of live births (0, 1–2, 3+ and unknown) and age at menarche (<13, 13, 14 + and unknown).

USA). Dietary intake, parity, BMI, smoking status and age at menarche did not differ between individuals who attended gynaecological examination and those who did not. The percentage of women who had had a prior diagnosis of fibroids did not differ between the two groups of women (15·0 *v.* 17·4 %).

## Results

Fifty-four women were identified as having fibroids (*n* 50) or having had a hysterectomy due to fibroids (*n* 4). The distribution of the size of the largest fibroid was nine (18·0 %), eight (16·0 %), eighteen (36·0 %) eleven (22·0 %), three (6·0 %) and one (2·0 %) for thumb-size, walnut-size, small goose egg-size, goose egg-size, large goose-egg size and fist-size, respectively. Distributions of non-dietary factors according to the prevalence of fibroids are shown in Table 1.

The OR of uterine fibroids was significantly increased in the highest tertile of alcohol compared with the lowest tertile (non-drinkers) after controlling for covariates (Table 2). There were no significant associations of intakes of fats,

dietary fibre and soya isoflavones with the prevalence of fibroids. Additional adjustment for alcohol intake did not alter these associations. Exclusion of women who had undergone a hysterectomy or women who had reported cramps (*n* 53) or abnormal bleeding (*n* 16) did not alter the results.

## Discussion

Despite the low alcohol intake in this present population, alcohol intake showed a significant positive association with uterine fibroids. Alcohol may have an oestrogenic action on the uterine myometrium. So far, three studies have addressed the association between alcohol intake and fibroids. A significant positive association was reported in two prospective studies, the Nurses' Health Study[7] and the Black Women's Health Study[8]. However, a case–control study of Italian women found no association with alcohol intake[6].

We expected that isoflavones would be inversely associated with fibroids. However, a somewhat increased OR for the second tertile of intake does not necessarily negate the possibility of a positive association between soya isoflavone intake and the risk of fibroids. We also failed to find significant associations between fibroids and intakes of fats and dietary fibre. Alcohol intake has been associated with increased serum oestrogen levels in women[5]. The associations of oestrogen levels with intakes of fats, dietary fibre and soya isoflavones have been inconsistently shown in previous studies[3,4,16]. These dietary components may not have sufficient effects to induce an oestrogen-like transcriptional response in the uteri.

The small number of subjects is a limitation of the present study. Although we had no evidence of any association between fibroids and intakes of fats, soya isoflavones and dietary fibre, we had insufficient power to detect a small but significant association. Another limitation is that the present study only identified prevalent, rather than incident, cases. Because the dietary questionnaire referred to habits during the year before the study, and because some proportion of the women with fibroids were those who had a history of hysterectomy, the dietary data for some cases may have reflected a time period after these cases were diagnosed. Some symptoms related to fibroids may make women change their diet. However, the exclusion of women who reported abnormal menstruation or bleeding did not substantially alter the results. In addition, the possible relationship between diet and fibroids was generally unknown to subjects.

Diet is likely to be associated with health behaviours such as participation in a gynaecological examination, which could result in the incidental detection of fibroids. Although studies with a prospective design are generally more efficient for the assessment of a cause–effect relationship, the results can be affected by detection bias unless the follow-up of fibroids status is not self-reported but is based on examinations uniformly conducted among all subjects. In the present study, the transvaginal ultrasound examination was used to determine the existence of fibroids for all subjects. The best practical tool available for epidemiological studies is transvaginal ultrasound, as it yields a much less selective set of cases than would be possible if pathological diagnosis were required[1]. A high sensitivity (99 %) and specificity (91 %) of ultrasound relative to pathological evidence have been reported[17].

The fact that our study subjects were participants in a health check-up programme is a concern. It is possible that, compared with women who eat a healthy diet, women with a less healthy diet are more likely to have a health check-up only when they are experiencing illness, including symptoms of fibroids. The observed positive association between alcohol intake and fibroids may have been affected by such a selection bias. However, diet as well as the percentage of women with a prior diagnosis of fibroids was similar between those who had selected the gynaecological check-up and those who had not.

In conclusion, data from the present study suggested that alcohol intake was associated with the prevalence of uterine fibroids. There was no evidence of a significant association of intakes of fats, soya isoflavones and dietary fibre with uterine fibroids. Further studies on diet, especially phytoestrogens, and uterine fibroids are needed, given the limited data currently available.

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# Development of Computer-Assisted Biohazard Safety Cabinet for Preparation and Verification of Injectable Anticancer Agents

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**Key Words**
Anticancer agents, preparation · Biohazard safety cabinet · Chemotherapy, cancer · Personal digital assistant · Safety management

**Abstract**
***Background:*** Medication errors associated with anticancer agents may cause fatal events. Therefore, exact verification of the prescription order and accurate preparation of the mixture of anticancer injections are required for safe management in cancer chemotherapy. ***Methods:*** A computer-assisted biohazard safety cabinet was newly developed for verification and preparation of anticancer agents. Using a barcode reader, information on prescription orders was transmitted from an electronic medical record to the computer system installed in the safety cabinet. The computer was controlled using a 3-button foot switch, which avoided interruption of the mixing procedure. A monitor on the cabinet wall displayed the required amounts of anticancer injections and any special information for the dissolution or mixing procedure. The names of anticancer agents were verified using a personal digital assistant and the volume of injection taken, which was automatically converted to weight on the basis of the specific gravity of anticancer solution, was recorded on the computer through a digital scale. ***Results:*** Accuracy and efficiency in mixing anticancer injections were compared between procedures with and without the present apparatus. Errors in the amounts were much smaller and the time spent in preparation was significantly shorter using the present apparatus. ***Conclusions:*** The present computer-assisted biohazard safety cabinet for preparation of the mixture of anticancer agents is considered to be potentially useful for the safe management in cancer chemotherapy.



## Introduction

The use of anticancer agents has greatly expanded in recent years as the rates of mortality and morbidity of cancer have increased. Consequently, aseptic preparation of a mixture of injectable anticancer agents has become one of major pharmaceutical practices. Sufficient care should be taken in mixing injectable anticancer agents to prevent exposure to mutagenic substances, to avoid bac-

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terial contamination and to prevent dispensing errors [1]. Anticancer agents have varying degrees of carcinogenic activity [2] and may pose a risk to the health of persons preparing them. Urinary carcinogenesis in pharmacists [3] and fetal damage in nurses [4] have been reported after exposure to anticancer agents. Carcinogenic anticancer agents are classified into 5 categories by the International Agency for Research on Cancer of the World Health Organization [5]. Absorption during preparation of cytotoxic agents is mainly via inhalation of evaporated or dispersed particles or direct skin contact with anticancer drugs [6]. Thus, the National Institutes of Health [7] and the American Society of Hospital Pharmacists [8] have recommended that anticancer injections should be prepared in a class IIB type biohazard safety cabinet, in which air pressure is negative relative to the surrounding areas and the inflow air from the preparation room through the high-efficiency particulate air filter exhausts without re-circulation to the outside after filtration.

Medication errors in cancer chemotherapy often cause serious outcomes, because of the narrow therapeutic range of a number of anticancer agents [9–13]. Thus, a complete check of each prescription is required. Moreover, it is important that anticancer agents are accurately mixed in the correct quantities, especially so for pediatric patients [14]. Computer-based order verification systems have been reported by several investigators [15–20], although few studies have applied such systems to the preparation of the mixture of cancer chemotherapy agents.

Skouroliakou et al. [17] have reported a computerized procedure for formulating total parenteral nutrition, which introduced automated composition calculation and a computer-driven device for formulation. However, to our knowledge, there have been no computer systems supporting verification and preparation of anticancer injections.

In the present study, we developed a novel biohazard safety cabinet, in which a computer system supporting the verification and preparation of the mixture of anticancer injections was incorporated. Subsequently, we evaluated the accuracy and efficiency of the apparatus compared to a conventional manual method of preparation of anticancer injections.

## Materials and Methods

*Components of a Biohazard Safety Cabinet*

The biohazard safety cabinet was a Class IIB apparatus. This class of equipment allows air to flow from the preparation room through the high-efficiency particulate air filter and exhausts it to the outside after filtration, without recirculation inside the cabinet. The apparatus was composed of a safety cabinet, in which the computer system with a 15-inch liquid crystal display, a foot-controlled 3-button switch, a digital scale and a barcode reader was installed. As shown in figure 1, the display was attached to the inner front wall of the cabinet, and the digital scale was linked to the computer system to verify the amount of injectable anticancer agents taken. To check the weight of injectable medicines, information about the specific gravity of each anticancer solution was obtained from pharmaceutical companies and they were recorded in the computer system. The barcode reader was set to recognize patients' data and information about anticancer prescription orders by reading a barcode label on the injection. The information about solvents for each anticancer agents and dissolution techniques were stored in the computer system. The monitor displayed relevant cautions, such as 'Ifosfamide injection (1 g) should be diluted with more than 25 ml of saline or distilled water' and 'Oxaliplatin injection (100 mg) should be diluted with 5% glucose solution'. The whole apparatus was placed in a clean room with a class 100 filling area where no particles (>0.5 mm in size) were detected as measured by a hand-held particle counter (Rion Corp.) on 6 occasions on different days.

*Computer Support System for Preparation of Injectable Anticancer Agents*

Patient information and prescription orders in the electronic medical database were transmitted to the computer system for preparation of injectable anticancer agents through the server in the pharmacy division. The amount of anticancer agents prepared was displayed. The names of pharmacists who prepared the anticancer mixture and those who were involved in verification of the mixture, and the date of preparation were recorded through a personal digital assistant (PDA). These data were stored on the server computer in the pharmacy division as well as in the electronic medical record system.

*Procedures for Dispensing and Mixing Injectable Anticancer Agents*

As shown in figure 2, the injection order and injection label were printed after prescription through the computerized order system. Pharmacists checked and verified the order on the basis of the chemotherapy regimens and patient information, which were obtained from the electronic medical record system by reading the barcode using a PDA. The anticancer agents were then transferred to the clean room where the biohazard safety cabinets were placed. The pharmacist in charge of the preparation of the mixture logged in to the computer system by entering the ID number. The list of all patients for whom injection orders were prescribed was displayed on the monitor in the cabinet (fig. 3). The contents of the prescription for the corresponding patient were displayed. Using the 3-button foot switch to move a cursor, the pharmacist retrieved patients' names and ID numbers, the ward, the date and time of prescriptions, and the names and amounts of injectable anticancer agents. On moving the cursor to the indication of an anticancer agent, the voice-reading system was activated, which spoke the name of the anticancer agent.

During the preparation of the mixture, information about the names and required amounts of anticancer agents was displayed. As a safety measure, alert messages were also shown where warranted. The dose of the anticancer agent was checked by the com-

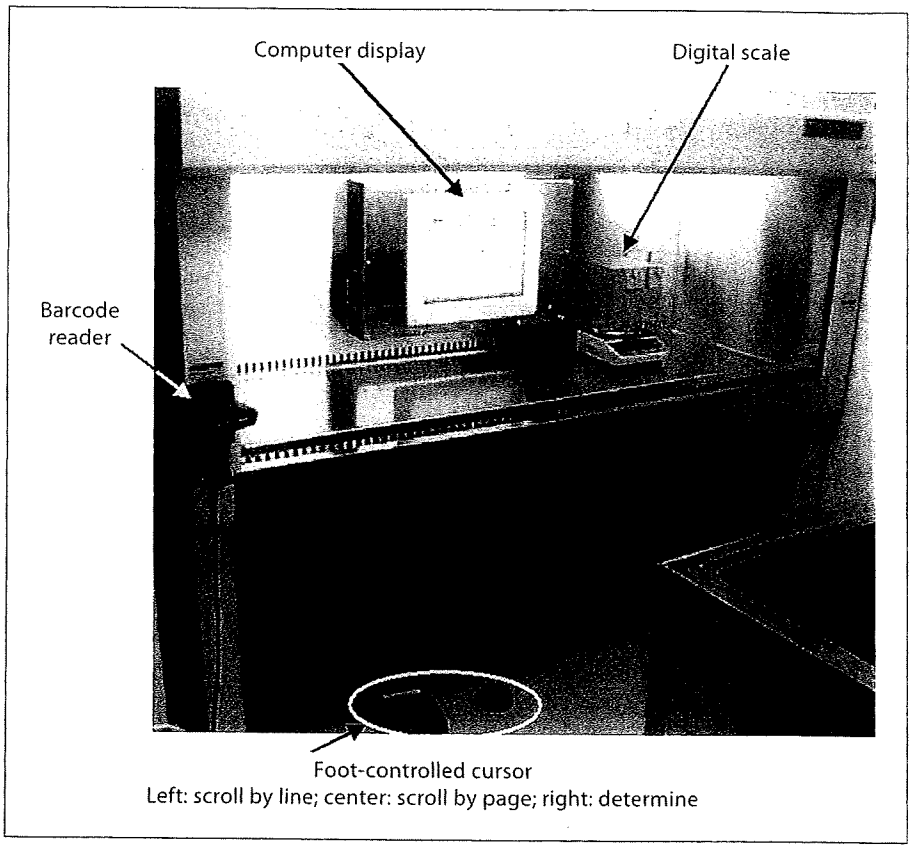


**Fig. 1.** Biohazard safety cabinet with a computer system that assists aseptic preparation and verification of injectable anticancer agents. A computer monitor was installed in the front wall of the cabinet. A digital scale, barcode reader, and 3-button foot switch were also incorporated into the system. The cabinet was placed in a clean room.

puter system by calculating the difference in the weight of the ampoule or bottle before and after the pharmacist had attempted to remove the desired amount. The required weight was calculated from the specific gravity of each injectable agent and was displayed on the monitor. The acceptable difference in the weight of the injection was within 5%. The amount of the injection was recorded in the computer (fig. 4 top). If the amount of the agent exceeds the permitted range, an alert message was displayed, and the pharmacist prepared the dose again. The preparation was verified by another pharmacist who also entered the system using the ID number (fig. 4 bottom).

*Comparison of Accuracy with and without the Present Apparatus*

The accuracy in preparing a certain amount of salicylic acid dissolved in saline or glycerol (viscous) solution was compared. The solution was prepared by the following two methods: a manual procedure and a procedure using the present apparatus. In the case of the manual procedure, the amount of agent prepared was checked visually by another pharmacist and the solution was prepared in volumes of 1, 2.5 and 5 ml using a 10-ml plastic syringe. To prepare powder preparation after dissolution and bubbly solution, 500 mg sodium salicylate was dissolved in 5 ml saline and 5 ml of 10% sodium laureth sulfate solution, respectively. Then, a 2.5-ml aliquot of saline solution or sodium laureth sulfate solution was taken using a 10-ml plastic syringe. The content of salicylic acid in either solution was determined by HPLC with spectrometric detection (OD at 296 nm) according to the method of Terweij-Groen et al. [21]. Data were statistically analyzed by Student's t test.

*Comparison of Efficiency with and without Present Apparatus*

To evaluate the efficiency of the present procedure, the time spent in preparing mixtures of solutions was compared between the procedures with and without present apparatus with regard to the liquid (etoposide injection, 5 ml) and powder (ifosfamide, 1 g) vial injections. In addition, the time spent preparing the mixtures, including dissolution of ifomide, calculation of the required amount of anticancer solution, verification of the amount taken with plastic syringe, and dilution in saline, was compared between a group of five pharmacists with more than one year of experience in the mixing procedures and a group of five of those who had less experience (<1 year). Data were statistically analyzed by paired t test.

## Results and Discussion

As shown in figure 5, the errors in the volume of salicylic acid increased in the procedure without using present apparatus, as the volume of solution prepared decreased (errors 3.4, 7.3 and 17.3% for 5, 2.5 and 1 ml, re-

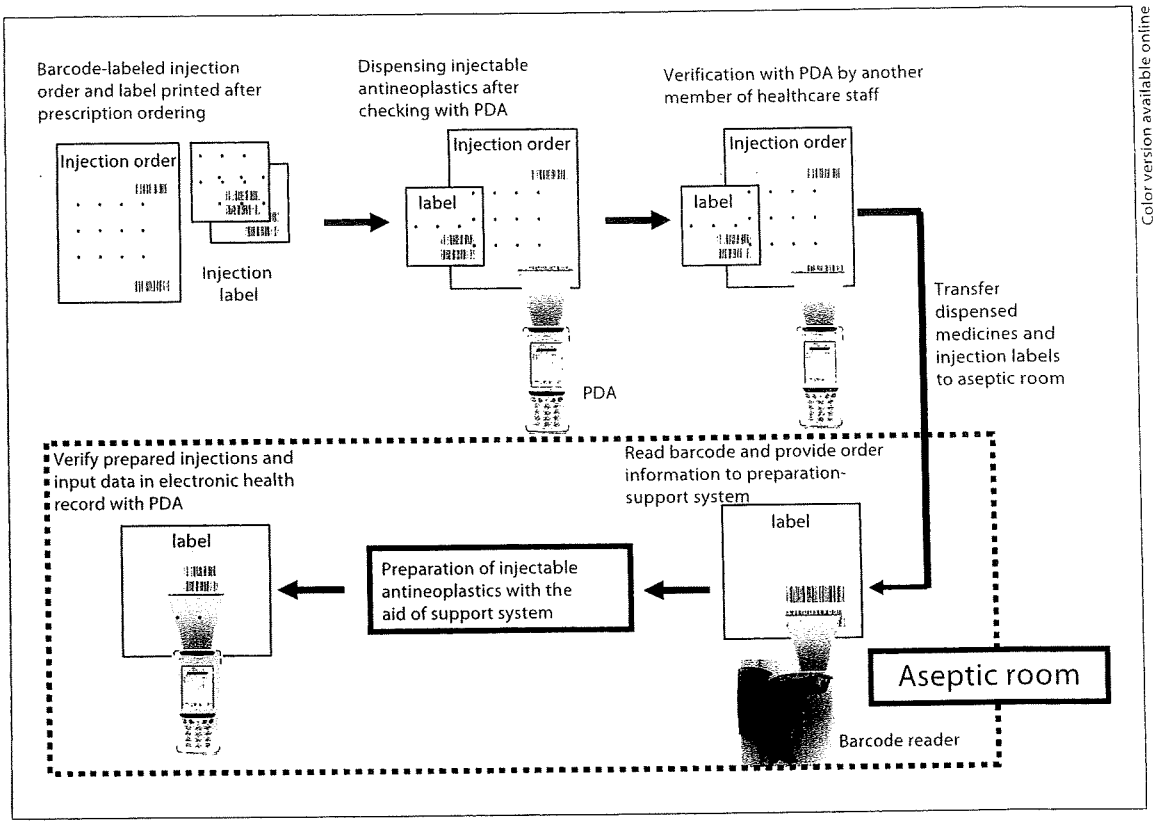


**Fig. 2.** Flowchart showing dispensing and preparation of injectable anticancer agents. An injection order and label were printed out following a prescription generated by the computerized order system. The injectable agents for each individual patient were transferred to the clean room where the biohazard safety cabinets were placed. Pharmacists prepared the mixture of injections using the computer-supported system and verified them with a PDA.

spectively). In contrast, the present apparatus yielded almost constant but much smaller differences in the weight irrespective of the volume taken (2.4–3.0%). In the present study, we used a 10-ml volume plastic syringe to take 1–5 ml solution to amplify the errors in the amount of collected samples. Even under such a condition, the method using the present apparatus enabled us to perform an exact preparation of anticancer injections.

We reported here for the first time the development of a computer-assisted biohazard safety cabinet for verification and preparation of anticancer injections, in which the required amount of medicines are automatically calculated and checked, and appropriate advice on the dissolution or dilution of some anticancer agents is indicated.

The amounts of anticancer agents markedly differ among prescription orders since the doses of anticancer agents are determined by the weight or the body surface area of the patient and/or the type of cancer. Systems that verify prescription and integrate drug information are considered helpful in reducing the incidence of preventable medication errors [22–26]. Errors in medication dosing during cancer chemotherapy can often result in serious problems, particularly in pediatric cases where even a small difference in the dose may be fatal [10, 14]. In this regard, the present apparatus for preparing the mixture of anticancer agents enabled us to accurately prepare the mixture regardless of the characteristics of the preparations (liquid solution, viscous solution, powder) or the required volume of a solution, compared to a conventional manual method. Therefore, the present computer-based method is assumed to potentially contribute to the safe management of cancer chemotherapy. Subsequently, the time needed to dispense the prepared mixture was compared with respect to liquid vial injection (etoposide, 5 ml) and powder vial injection (ifosfamide, 1 g). As shown in figure 6a, the time spent in preparing the mixture from liquid solution, powder preparation after dis-

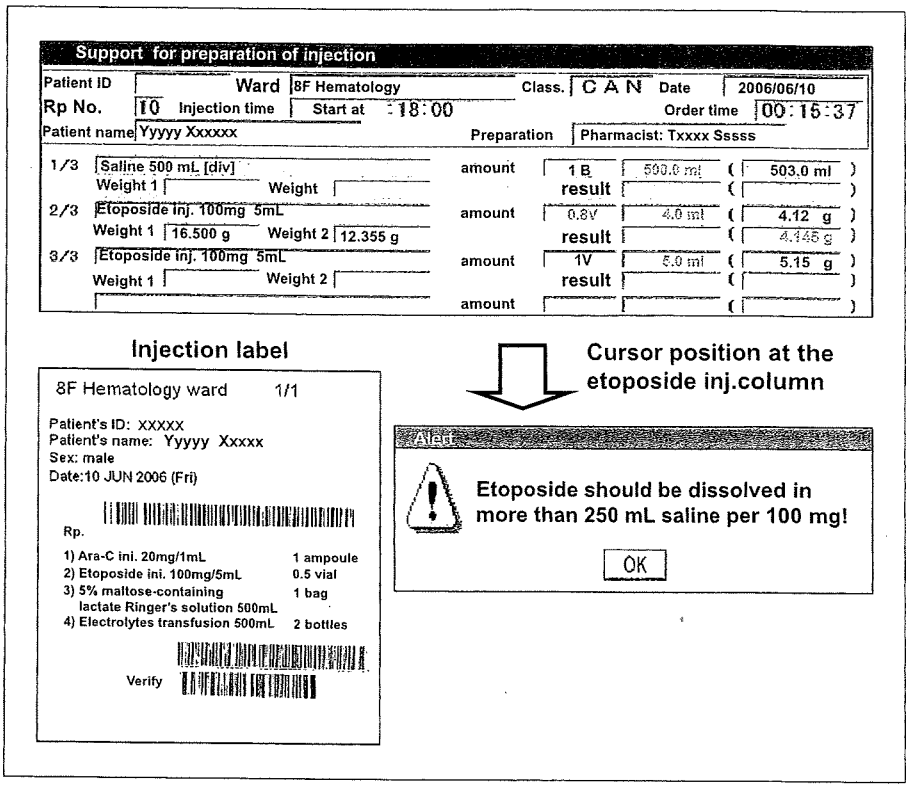


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**Fig. 3.** Representative display showing the required amount of anticancer agent (etoposide) assisted by the computer system supporting preparation and verification for mixing of injectable anticancer agents. The amount of anticancer agent was checked by the system from the difference in the weight of the ampoule or bottle before and after taking the injection. An alert message regarding mixing procedure, such as the volume of diluting solution, is shown. Printed on the injection label are the patient's name, sex and ID number, the date of prescription and the names and amounts of the anticancer agents together with transfusions in the chemotherapy regimen.

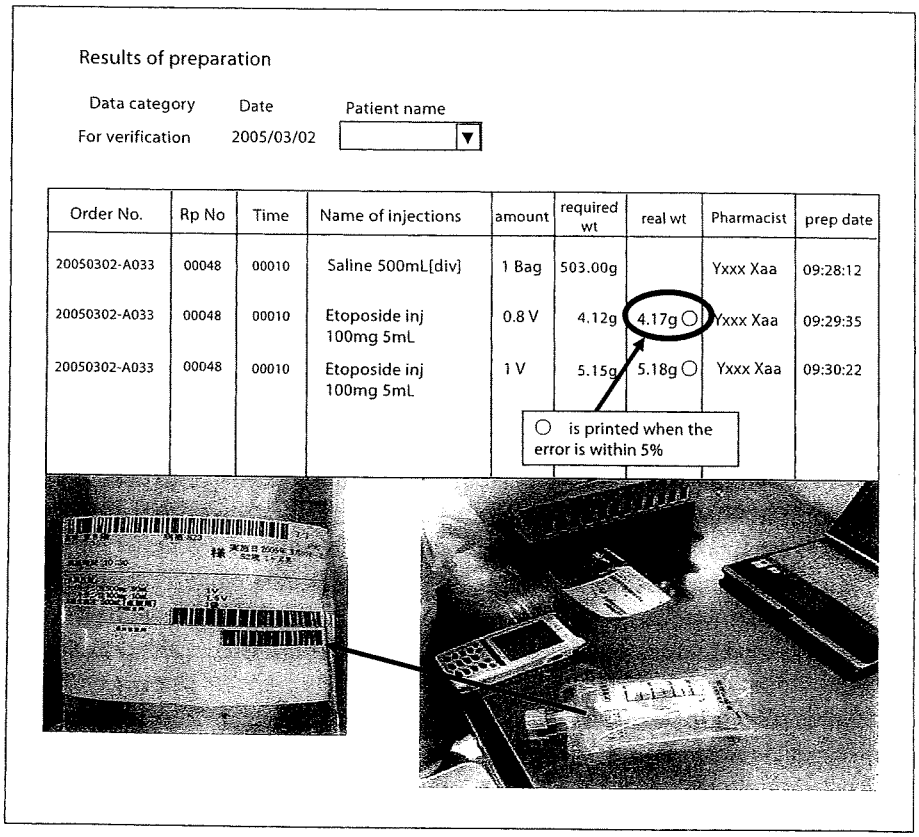


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**Fig. 4.** Verification of prepared injections. The information about the preparation of injectable anticancer agents can be obtained with the PDA by reading the barcode printed on the injection label, which is put on the plastic container after preparation. Another member of the healthcare staff verifies the prepared injection by checking the item and the amount of the anticancer agents on the monitor of the preparation-verify system computer.

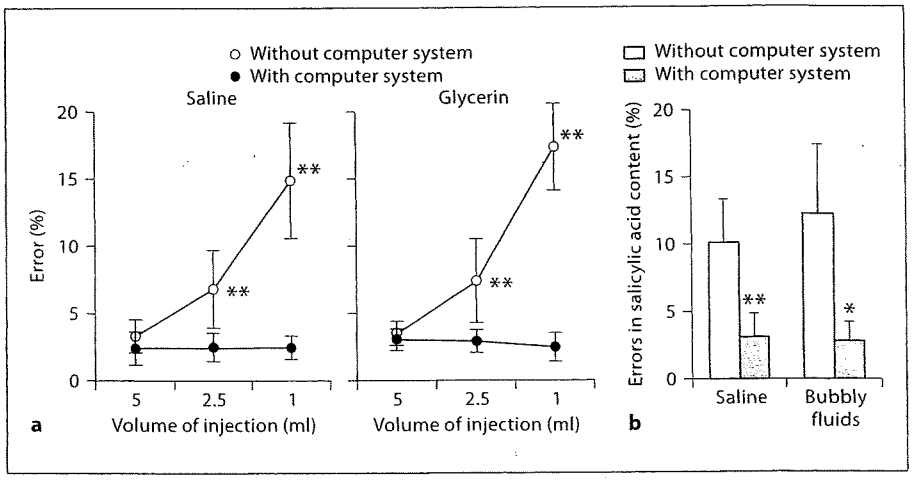


**Fig. 5.** Comparison of the errors in the volume of fluids (**a**) and the concentration of salicylic acid (**b**) prepared from saline or glycerin solution containing salicylic acid (2.5 ml) between the study and conventional methods. In the conventional method, the fluid volume in the plastic syringe was checked by another staff member. Data represent the mean ± SD of 10 (**a**) or 5 (**b**) experiments. * $p < 0.05$; ** $p < 0.01$ (Student's t test).

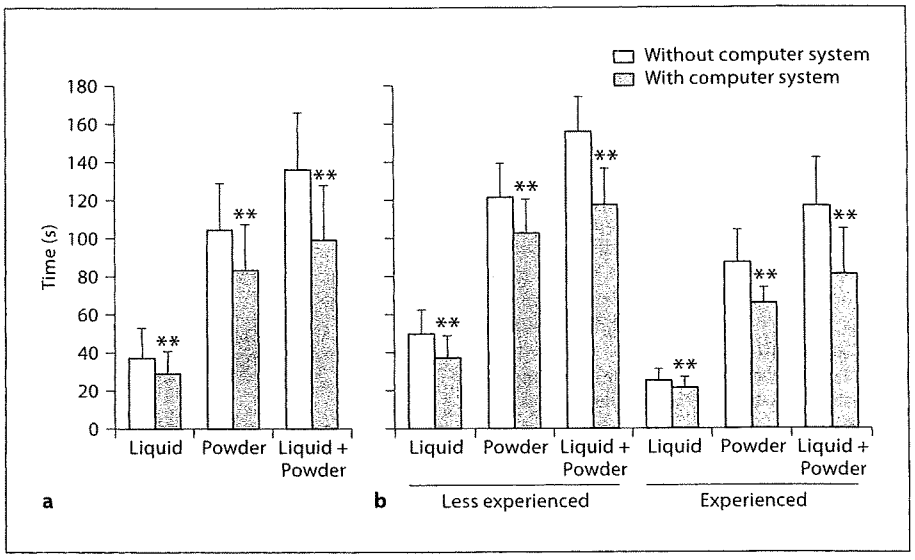


**Fig. 6.** Comparison of the time spent in preparing injectable mixture from liquid ampoules, powder vials or both, before and after introduction of the present study system. Data were obtained from 5 experienced (>1 year) and 5 less experienced (<1 month) pharmacists, and were expressed totally (**a**) or separately (**b**). Each pharmacist prepared the mixtures with and without the study's computer-support system. Data represent the mean ± SD. ** $p < 0.01$ (paired t test).

solution or both, was shorter in the present method than in the conventional method without using the computer-assisted system. This pattern was observed both in the less experienced (<1 year) and more experienced (>1 year) pharmacists (fig. 6b). This may be due to the fact that it took longer in the conventional manual method to calculate the amount of injection based on the patient's body surface area and to verify visually the volume of liquid injection or solution collected into the plastic syringe by another practitioner, as compared to the method using computer-assisted apparatus. Thus, we considered that the total time spent preparing anticancer injections was shorter in the present method than in the conventional manual method. Thus, the present method may enhance the efficiency in mixing procedures of chemotherapy agents. This may be due to the improvement of the task in which the pharmacists prepare the mixture according to the directions displayed on the monitor by operating the computer cursor with a foot switch, thereby not interrupting the mixing procedure itself. This method also enabled us to prevent environmental pollution by anticancer agents. In the conventional method for preparing the mixture of anticancer agents, the volume of injections to be delivered by a staff member should be confirmed visually by another staff member to ensure safety management in cancer chemotherapy. In the present system, the doses of injections to be delivered were checked by the computer system, thereby minimizing labor costs. Indeed, there have been no dispensing errors in the anticancer injections in the pharmacy division in the first 6 months after introduction of the present apparatus, during which a total of 4,844 prescriptions were ordered.

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Research paper

# Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy

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ABSTRACT

We prepared fast dissolving oral thin film that contains dexamethasone and base materials, including microcrystalline cellulose, polyethylene glycol, hydroxypropylmethyl cellulose, polysorbate 80 and low-substituted hydroxypropyl cellulose. This preparation showed excellent uniformity and stability, when stored at 40 °C and 75% in humidity for up to 24 weeks. The film was disintegrated within 15 s after immersion into distilled water. The dissolution test showed that approximately 90% of dexamethasone was dissolved within 5 min. Subsequently, pharmacokinetic properties of dexamethasone were compared in rats with oral administration of 4 mg dexamethasone suspension or topical application of the film preparation containing 4 mg dexamethasone to the oral cavity. Pharmacokinetic parameters were similar between the two groups in which $C_{max}$ (h), $T_{max}$ (μg/mL), AUC (μg/mL/h) and half-life (h) were 12.7 ± 6.6 (mean ± SD, $N = 10$), 3.4 ± 1.4, 93.6 ± 37.8 and 1.66 ± 0.07, respectively, for oral suspension and 13.3 ± 4.0, 3.2 ± 1.0, 98.0 ± 22.3 and 1.65 ± 0.06, respectively, for film preparation. These findings suggest that the fast dissolving oral thin film containing dexamethasone is likely to become one of choices of dexamethasone preparations for antiemesis during cancer chemotherapy.



## 1. Introduction

The fast dissolving oral film preparation is a new drug delivery technique to provide medicines to patients with obstacles in swallowing or under emetic condition during cancer chemotherapy. The morbidity and mortality of cancer have been increasing and thus the number of patients who receive cancer chemotherapy has been elevated in the recent years. However, a number of patients who undertook cancer chemotherapy complain of side effects associated with anticancer drugs. Among them, nausea and vomiting are one of the most frequent side effects. Nausea and vomiting induced by emetogenic anticancer drugs include acute and delayed events, in which acute emesis occurs within a day of chemotherapy, while delayed event appears after 24 h and persists for several days [1–8]. According to the guidelines for prevention of cancer chemotherapy-induced emesis documented by Multinational Association of Supportive Care in Cancer (MASCC) [9], American Society of Clinical Oncology (ASCO) [10], and National Comprehensive Cancer Network (NCCN) [7], 5-$HT_3$ receptor antagonist, dexamethasone and/or neurokinin $NK_1$ receptor antagonist aprepitant are recommended to use in combination before chemotherapy for prevention of acute emesis, and dexamethasone alone or in combination with aprepitant is encouraged to administer orally for prophylaxis of the delayed emesis induced by high to moderate risk of emetogenic anticancer drugs. On the other hand, disturbance in eating and swallowing associated with oral mucositis is often encountered in patients with head and neck cancer who underwent combination of chemotherapy and radiotherapy [11–14]. Therefore, the antiemetic oral medicines are inconvenient to use in such patients.

Oral disintegrating tablets [15,16] and oral jerry preparations [17] have been developed for patients with dysphagia or aphagia. The jerry preparations have an advantage of taking without choke and are useful for elderly patients but are bulky in many cases,

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while oral disintegrating tablets are readily disintegrated but the disintegrated materials are insoluble and remain until swallowing. On the other hand, edible thin oral film preparations have been used as oral care products [18,19]. These preparations easily dissolve in saliva, thereby requiring no water to take. Therefore, the oral disintegrating thin film preparation appears to be useful for patients with eating and swallowing disturbance.

In the present study, we developed a fast-disintegrating oral thin film containing dexamethasone. The content uniformity and stability were tested. We also investigated the pharmacokinetic characteristics in rats with topical application of the film preparation to the oral cavity.

## 2. Materials and methods

### 2.1. Materials

Dexamethasone and ethyl-*p*-hydroxybenzoate were obtained from Nacalai Tesque (Kyoto, Japan). Microcrystalline cellulose (Asahikasei Co. Ltd., Tokyo, Japan), polyethylene glycol (Sanyo Chemical Industries, Ltd., Kyoto), polysorbate 80 (Nichiyu Co., Ltd., Tokyo), 5% low-substituted hydroxypropyl cellulose (L-HPC) and hydroxypropylmethyl cellulose (hypromellose) (Shin-Etsu Chemical Co., Ltd., Tokyo) were used as film base materials.

### 2.2. Preparation of oral film

The constituents of the basic materials were microcrystalline cellulose (57%), polyethylene glycol (15%), hypromellose (7.4%), polysorbate 80 (5.4%) and 5% L-HPC (1.3%). The bases of the film preparation were mixed and fragrance ingredients were included, then the mixture was coated onto plastic film to prepare thin film, then dried by heating. The resultant film was cut into the four-square of 2 cm × 2 cm in size, in which 4 mg dexamethasone was included.

### 2.3. Uniformity of dosage units of the preparation

The uniformity of dosage units of the oral film preparation was tested using 20 preparations, and the content of dexamethasone was determined by HPLC with spectrometric detection. The acceptance value (*AV*) of the preparation is less than 15%, according to the JP15. *AV* for JP15 was calculated according to the following equation:

$$AV = |M - X| + ks, \quad (1)$$

where $M$ is label claim (100%), $X$ is the average (%) of individual contents, $k$ is the acceptability constant (2.2), $s$ is the standard deviation.

In USP27, the contents of major component in the preparation should be within a range between 85% and 115%, and the relative standard deviation should be less than or equal to 6.0%.

### 2.4. Sample preparation

A piece of oral film containing 4 mg dexamethasone was dissolved in 100 mL of 50% methanol solution. One-milliliter aliquot of the solution was transferred to a polypropylene tube and 1 mL of ethyl-*p*-hydroxybenzoate (40 μg/mL) was added as the internal standard. Then, mobile phase was added to the mixture and the volume was adjusted exactly to 10 mL.

### 2.5. Stability test

A piece of film preparation was stored in an aluminum package at 25 °C with 50–60% humidity (normal condition) or at 40 °C with 75% humidity (accelerated condition) for 4–24 weeks, then the content of dexamethasone was determined. In addition, the film sample was subjected to the dissolution test.

### 2.6. Dissolution test

The dissolution test was performed according to the JP15 paddle method using the paddle apparatus (NTR-6000, Toyama Sangyo Co., Ltd., Osaka, Japan). Test solution was 900 mL of phosphate solution (pH 1.2) at 37 ± 0.5 °C with a rotation rate of 50 rpm. Ten-milliliter aliquot of samples was taken from 2 min to 60 min with autosampler (PAS-615, Toyama Sangyo Co., Ltd.) and the same volume of fresh test solution was replenished. One-milliliter aliquot of samples was taken in a polyethylene tube and the same volume of the internal standard solution (4 μg/mL) was added, and 50-μL aliquot of the mixture was injected onto HPLC to determine the concentration of dexamethasone.

### 2.7. Determination of pharmacokinetic parameters in rats

Seven-week-old male Sprague–Dawley rats were used in the present experiment. The animals were housed in a room maintained on a 12-h light/dark cycle at 23 ± 2 °C with free access to food and water. The experimental procedures were approved by the Committee for the Care and Use of Laboratory Animals at the Gifu Pharmaceutical University. Under light ether anesthesia, rats were orally given with 4 mg of dexamethasone suspension in a volume of 0.5 mL or topically applied with the film (2 cm × 2 cm) containing 4 mg of dexamethasone to the oral cavity. The film was cut into two pieces (1 cm × 2 cm) and applied to the inner cheeks bilaterally. Blood specimens were taken (every 0.25 mL) in a heparinized glass capillary tube from the tail vein at 15 min, 30 min, 1 h, 2 h, 3 h, 6 h, 12 h, 24 h and 48 h after drug administration. After centrifugation at 10,000 rpm for 5 min, plasma was taken in a polyethylene tube and stored at −70 °C until assay. The concentration of dexamethasone was determined by HPLC with spectrometric detection using ethyl-*p*-hydroxybenzoate as the internal standard. The HPLC system was LC-VP system (Shimazdu Co. Ltd, Kyoto) with the reversed-phase ODS separation column (Symmetry C18, 4.6 × 250 mm, Nihon Waters, Tokyo). The mobile phase was a mixture of 0.01 M potassium phosphate buffer (pH 7.0) and acetonitrile (55:45% v/v) and delivered at a flow rate of 1.0 mL/min. A 50-μL aliquot of sample was injected directly onto HPLC and dexamethasone was detected from the absorbance of OD at 240 nm.

### 2.8. Validation of analysis

The calibration curve for dexamethasone was plotted in triplicate using eight different concentrations of rat serum spiked with 0.1, 0.25, 0.5, 1, 5, 10, 25 and 50 μg/mL of dexamethasone.

### 2.9. Statistical analysis

Data were expressed as the mean ± SD. In the stability test and dissolution study, data were analyzed and statistically compared by Dunnett's test. Data on the pharmacokinetic parameters were compared between two groups and statistically evaluated by *t*-test.

## 3. Results and discussion

### 3.1. Uniformity of dosage units of oral film preparation

The average of dexamethasone content in 20 preparations was 3.97 ± 0.16 mg and the values were ranging from 93.4% to 106.2%. The relative standard deviation was 4.4%. Thus, the preparation met the criteria of USP27 content uniformity. Moreover, *AV* was 11.8%, a value that was within the limit (15%) of uniformity of dosage units for JP15.

### 3.2. Stability

When the oral film preparation was stored in an aluminum package under normal condition or in a chamber controlled at 40 °C and 75% in humidity for 4–24 weeks, no apparent changes in the dexamethasone content, form or color of preparations were observed. The contents of dexamethasone were fairly stable ranging from 92.4% to 102.7% during 24 weeks after storage at 25 °C and 50–60% humidity (normal condition), or from 98.0% to 103.4% during the same periods after storage at 40 °C and 75% humidity (accelerated condition) (Fig. 1).

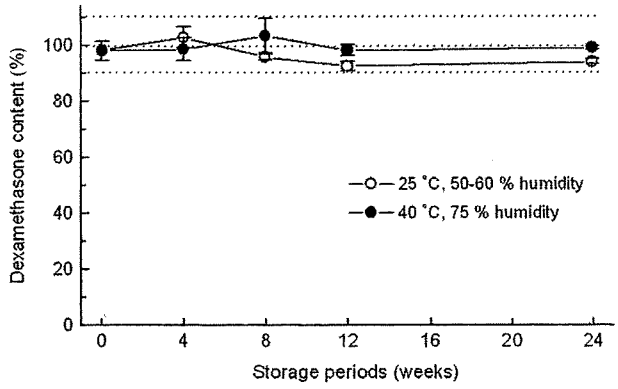


**Fig. 1.** Stability of the fast dissolving oral film containing dexamethasone after storage under normal condition (A) or accelerated condition (B) for up to 24 weeks. Each film was wrapped in an aluminum package and stored at 25 °C with 50–60% humidity (normal condition) or at 40 °C with 75% humidity (accelerated condition). Each column represents the mean ± SD of 10 experiments. Data were statistically analyzed by Dunnett's test.

### 3.3. Dissolution of film preparation

Disintegration of film was checked by immersion of the film into distilled water and the time to disintegrate was 12.5 ± 1.3 s (mean ± SD, $N = 6$). On the other hand, the dissolution test was performed using pH 1.2 phosphate buffer solution since dexamethasone is more stable in a slightly acidic pH condition. As shown in Fig. 2, a rapid dissolution of the film preparation was observed by the dissolution test, in which approximately 90% of dexamethasone dissolved within 5 min. Notably, the dissolution profile was similar among preparations stored for 0–24 weeks in aluminum packages. Chambin et al. [20] have shown that addition of microcrystalline cellulose to the tablet increases dissolution rate, although the compound itself is not soluble in water, while addition of hydroxypropylmethyl cellulose reveals the steady dissolution. Therefore, the rapid dissolution of the present film preparation may be due to the inclusion of high amounts of microcrystalline cellulose in the preparation (more than 50%).

### 3.4. Comparison of pharmacokinetic parameters between oral solution and oral film in rats

Fig. 3 shows the time course of changes in dexamethasone concentrations in rat plasma after oral administration of dexamethasone suspension or topical application of the fast-disintegrating film to the oral cavity. The pattern of changes in plasma concentrations was similar between the two groups. The pharmacokinetic parameters such as $T_{max}$, $C_{max}$, $AUC_{(\infty)}$, Ke, $t_{1/2}$, $Cl_{tot}$ and steady-state Vd were thus comparable between the two groups (Table 1).

The present fast-disintegrating film met the criteria of *AV* in the dosage uniformity test for JP15 and USP27. The content of dexamethasone was stable for at least 24 weeks after preparation, even stored at 40 °C and 75% humidity. The film also showed a rapid disintegration and dissolution profile of dexamethasone. In rats, plasma concentration of dexamethasone increased after topical application of the film preparation to the oral cavity, in which the peak appeared at 3.4 h with a $C_{max}$ value of 12.66 mg/mL and area under curve of 93.64 mg/mL/h. Similar pharmacokinetic parameters were obtained from rats with oral administration of dexamethasone suspension. One of the advantages of oral film preparation is the ease to intake without water. The base materials used in the present film preparation have been applied to oral care products and food additives, thus the safety of the materials was certified. Thus, the present film containing dexamethasone can

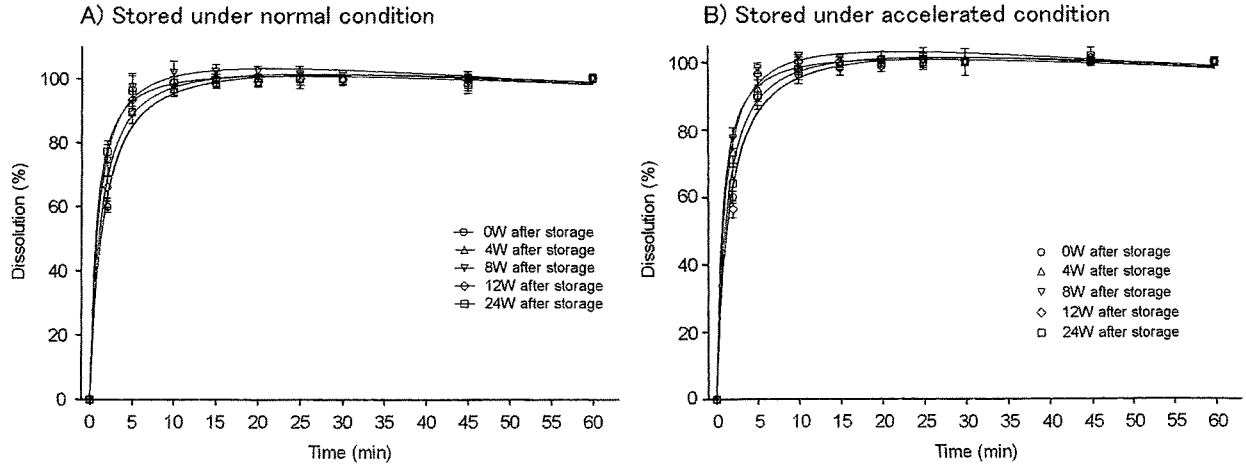


**Fig. 2.** Dissolution profile of dexamethasone-containing film stored for up to 24 weeks under normal (A) and accelerated conditions (B). Each film was wrapped in an aluminum package and stored at 25 °C with 50–60% humidity (normal condition) or at 40 °C with 75% humidity (accelerated condition). Each point represents the mean ± SD of six experiments. Data were statistically analyzed by Dunnett's test.

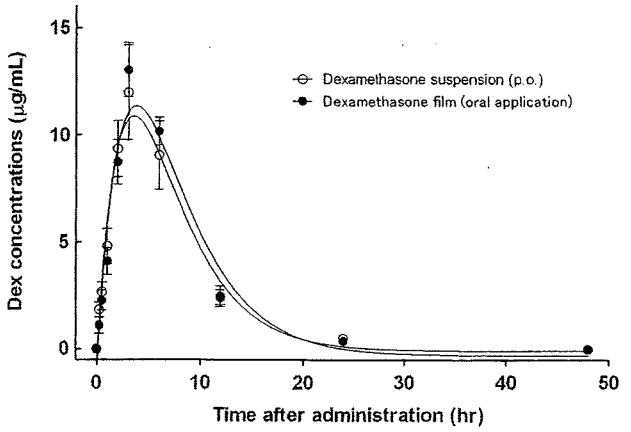


**Fig. 3.** Comparison of time course changes in plasma concentration of dexamethasone administered with oral film or suspension in rats. Rats were lightly anesthetized with ethyl ether and dexamethasone was administered orally with solution or ingested with oral film preparation at a dose of 5 mg. Each point represents the mean ± SD of 10 animals.

**Table 1**
Comparison of pharmacokinetic parameters of dexamethasone between oral film and oral suspension in rats.

| | Oral film ($N = 10$) | Solution ($N = 10$) | $P$ values |
|---|---|---|---|
| $T_{max}$ (h) | 3.20 ± 1.03 | 3.40 ± 1.43 | 0.724 |
| $C_{max}$ (μg/mL) | 13.33 ± 3.97 | 12.66 ± 6.61 | 0.785 |
| $AUC_{(\infty)}$ (μg/mL/h) | 98.01 ± 22.28 | 93.64 ± 37.75 | 0.756 |
| ke ($h^{-1}$) | 0.42 ± 0.01 | 0.42 ± 0.02 | 0.713 |
| $T_{1/2}$ (h) | 1.65 ± 0.06 | 1.66 ± 0.07 | 0.696 |
| $Cl_{tot}$ (L/h) | 0.05 ± 0.01 | 0.06 ± 0.02 | 0.410 |
| $Vd_{ss}$ (L) | 0.37 ± 0.12 | 0.44 ± 0.20 | 0.344 |

$T_{max}$ and $C_{max}$ were determined from individual real value. Each value represents the mean ± SD.

be applicable to patients with difficulties in oral intake, particularly to patients who need antiemetic therapy during cancer chemotherapy. On the other hand, oral steroid film may sometimes cause several side effects such as irritation of the oral mucosa, hoarseness, bacterial or fungal infections. To minimize the risk of such side effects in clinical setting, patients are sure to rinse thoroughly or gargle after taking the present dexamethasone-containing oral film.

Several lines of evidence have shown that stimulation of 5-$HT_3$ receptors is implicated in the etiology of chemotherapy-induced acute emesis: serotonin release from intestinal enterochromaffin cells, as evidenced by the increase in urine and plasma levels of 5-hydroxyindole acetic acid, a major metabolite of serotonin, is elevated after high doses of cisplatin [21], several 5-$HT_3$ receptor antagonists are effective for prophylaxis of acute but not delayed emesis induced by high- or moderate-emetogenic anticancer drugs [21,22]. On the other hand, glucocorticoids such as dexamethasone is effective for prevention of acute as well as delayed emesis in patients who received a high dose of cisplatin [23,24]. Moreover, dexamethasone causes a more marked antiemetic effect against acute and delayed emesis, when used in combination with the 5-$HT_3$ receptor antagonist [4,25]. Although the precise mechanisms underlying the antiemetic action of dexamethasone remain to be clarified, Malik et al. [26] have shown in rats that cisplatin increased, while dexamethasone decreased, acylated form of ghrelin, an endogenous orexigenic peptide that stimulates gastric motility in plasma, suggesting a possible involvement of ghrelin modulation in the antiemetic action of dexamethasone. Several clinical practice guidelines for antiemesis during cancer chemotherapy have recommended the use of dexamethasone on days 1–4 of chemotherapy. For outpatients, oral preparation of dexamethasone is usually prescribed but is hard to use for patients with difficulties in intake due to emetic symptoms or oral inflammation. In this regards, the present fast dissolving oral film seems to be potentially useful for such patients.

## 4. Conclusion

We prepared for the first time a fast dissolving oral thin film containing dexamethasone. The preparation revealed excellent uniformity and stability of dexamethasone and rapidly disintegrated in water. There were no significant differences in pharmacokinetic parameters obtained from rats with oral administration of dexamethasone suspension and those with topical application of the film to the oral cavity. Therefore, the present fast-disintegrating oral film containing dexamethasone is considered to be potentially useful for cancer patients with disturbance in eating and swallowing who receive radiotherapy and/or high- to moderate-emetogenic anticancer drugs.

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[原著]

# 大学生の健康に対する取り組みと生活環境に関する検討

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**要旨**：大学生世代は，入学を機に単身生活を始め，健康面や経済面をも含めた基本的な生活を初めて自己管理するようになる時期であるが，どの程度健康を意識して，生活に反映させているかに関する調査報告はほとんどない。このため，今回我々は大学生の健康に対する取り組みと生活環境を調べるために質問調査を実施した。

対象は，平成21年度定期健康診断を受診した岐阜大学生6,288名であり，健康に対する取り組みの有無や副業，睡眠，疲労感等の生活状況についてアンケート調査を行った。本検討では，調査に同意し回答の得られた4,657名の結果を解析した。

結果では，「健康のために時間やお金をかけている」と回答した学生は799名（17.2%）であり，女性で有意に多かった。取り組みの内訳は多いものより，「サプリメント（402名）」「健康食品（154名）」「筋トレ（121名）」「マッサージ（79名）」の順であった。副業をしている学生は2,830名（60.8%）であり，副業の有無により睡眠時間に有意な影響が認められた。

調査学生の約１／６が健康のために時間やお金をかけているが，多くはサプリメントや健康食品等の摂取によるものであった。

以上より，学生の健康支援のために，食品や栄養に関する正しい情報提供や，無理の無い運動，ストレッチ方法等の紹介，あるいは日常スケジュール管理に関する指導等の推進が今後ますます求められているものと考えられた。

**キーワード**：健康維持，補完代替医療，学校保健

## はじめに

大学生世代は，健康を大きく崩すことが少なく，学業やスポーツのみならず，副業などの社会活動への関心が高まり，成人として社会に出る準備をする大切な時期である。一方で，入学を機に単身生活を始め，健康面や経済面をも含めた基本的な生活を初めて自己管理するようになる時期でもある。にもかかわらず，学生がどのように健康を意識して生活しているかに関する調査報告はこれまでほとんどなされていないのが現状である。学生が，健康や肥満防止，疲労回復など様々な目的で行っている健康に対する取り組みは種々洋々であり，保健管理センター等健康管理専門職員から，適切な指導や助言を行った方が良い内容もあると思われる。

以上より，今回我々は，健康への取り組みと副業や睡眠等の生活環境を調べるために，質問調査を実施した。

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## 対象と方法

平成21年度定期健康診断を受診した岐阜大学生6,288名（2009年5月31日現在）を対象に健康に対する取り組みの有無や副業や睡眠，疲労感等の生活状況についてアンケート調査を行った。本検討では，調査に同意し回答の得られた4,657名（男性2,827名，女性1,830名，回収率74.1％）の結果を解析した。統計ソフトはStat View5.0を使用した。質問は，Q1「健康のために，時間やお金をかけていますか？」，Q2「Q1で『はい』の人へ，何に取り組んでいますか？」，Q3「疲労をどの程度感じますか？」，Q4「毎日の睡眠時間はどれくらいですか？」，Q5「生活の中で副業をしていますか？」の項目とした（表1）。アンケート調査は，定期健康診断の問診票の一部として組み込み，Web上で配信と回答両方を行った。検討および個別の情報処理にあたり，プライバシーの配慮に留意した。本調査は岐阜大学大学院医学系研究科倫理審査の承認を得ている。

Q1　健康のために時間とお金をかけていますか？

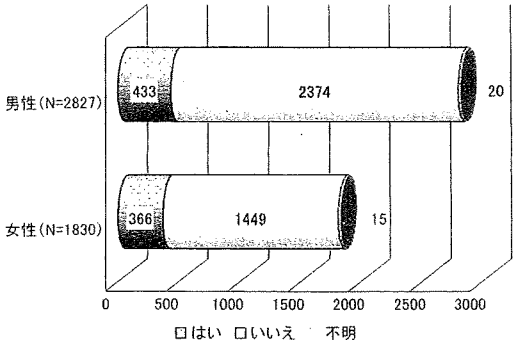


図1

表1　平成21年度学生定期健康診断時アンケート質問表

Q1　健康のために時間やお金をかけていることはありますか？
（　）はい　（　）いいえ
Q2　Q1で『はい』の人へ、何に取り組んでいますか？
（　）サプリメント　→　どんなものですか？　（　　）
（　）健康食品　　→　どんなものですか？　（　　）
（　）カイロプラクティック
（　）ヨガ　（　）リラックス法　（　）ヒーリング
（　）漢方薬　（　）鍼灸　（　）耳ツボ療法
（　）その他　→　どんなものですか？　（　　）
Q3　疲労をどの程度感じますか？
（　）ひどく疲れている　（　）疲れている　（　）時々疲れを感じる
（　）疲れていない
Q4　毎日の睡眠時間はどれくらいですか？
（　）5時間未満　（　）5～7時間　（　）7～9時間
（　）9～11時間　（　）11時間以上
Q5　生活の中で副業をしていますか
（　）している　→（週に　　日　　延べ　　時間）
（　）していない

表2　Q2　Q1で「はい」の方，何をしていますか？（複数回答可）

| | | |
|---|---|---|
| サプリメント　402人 | 健康食品　154人 | 筋力トレーニング（縄跳び，踏み台昇降，軽い運動，ランニング，ストレッチ，ロデオボーイ，コアリズム）　121人 |
| マッサージ　79人 | 部活・スポーツ　38人 | リラックス法　37人 |
| 漢方薬　33人 | ヨガ　31人 | カイロプラクティック　19人 |
| 食生活を見直す　14人 | 水泳　9人 | 整体・接骨院　7人 |
| 鍼灸　7人 | 処方薬　6人 | 温泉・サウナ・岩盤浴　6人 |
| 自転車・徒歩通学　5人 | 耳つぼ療法　4人 | 栄養ドリンク　3人 |
| リフレクソロジー　2人 | 散歩　2人 | Wii Fit　2人 |
| その他 | | |

## 結　果

Q1の問い「健康のために時間やお金をかけていますか？」に，「はい」と回答した学生は，799名（17.2％，男性433名，女性366名）であった。欠測者を除き男女差について$\chi^2$検定を行ったところ，女性で有意に多かった（図1）。

Q2で設問の取り組みの内訳は調査項目では多いものより，「サプリメント（402名）」「健康食品（154名）」「筋力トレーニング（121名）」「マッサージ（79名）」の順であった（表2）。その他では回答者が2人以上の項目で「部活・スポーツ」「リラックス法」「漢方薬」「ヨガ」「カイロプラクティック」「食生活の見直し」「水泳」「整体・接骨院」「鍼灸」「処方薬」「温泉・サウナ・岩盤浴」「自転車・徒歩通学」「耳つぼ療法」「栄養ドリンク」「リフレクソロジー」「散歩」「Wii Fit」が見られた。独力で行う健康法から，専門家のもとにて有料で行う施術まで多彩な回答が認められた。

Q3の疲労に関する質問では「ひどく疲れている」が109名，「疲れている」が788名，「時々疲れを感じる」が2,854名，「疲れていない」が872名であった（表3）。性別や副業の有無による差は認められなかった。

Q4の睡眠時間に関する質問では「5－7時間」が3,459名と最も多かった（表4）。