field may therefore have led to a better outcome than those in other reports.

Many studies have reported on chemoradiotherapy followed by surgery vs. surgery alone. Recent randomized studies found conflicting results. Bosset *et al.* (17) did not find any overall survival benefit with the addition of preoperative CDDP and 37 Gy of radiation to esophagectomy in squamous cell carcinoma of the esophagus. Urba *et al.* (18) also reported no statistically significant difference in survival between preoperative chemoradiotherapy vs. surgery alone for resectable esophageal cancer. Burmerster *et al.* (19) also reported no difference in overall survival between preoperative chemoradiotherapy followed by surgery and surgery alone. Our results also showed that definitive chemoradiotherapy had comparable survival to radical surgery alone for esophageal cancer. Thus, it is uncertain whether preoperative chemoradiotherapy may provide a better survival for esophageal cancer patients than surgery or definitive chemoradiotherapy alone. Additional studies are needed to clarify these controversies in the treatment of esophageal cancer.

The site of failure in the chemoradiotherapy group was different from in the surgery group. In the chemoradiotherapy group, it was local in 18 patients, local and regional lymph nodes in 1, and distant metastasis in 4 patients. In the surgery group, it was local in 1 patient, regional lymph nodes in 4, and distant metastasis in 14. It is uncertain whether the future combination of these modalities will obtain better survival for esophageal cancer patients, because of the more frequent complications of salvage surgery after chemoradiotherapy with a radiation dose of 60 Gy and frequent distant metastasis after surgery.

We investigated the food content and body weight of the patients in terms of the patients' status both before and after treatment. In our results, the status after treatment was better for the chemoradiotherapy group than for the surgery group, with a statistically significant difference. It has been reported that 90% of patients after esophagectomy lost weight compared with their preoperative status at 3 months, and only 10% of the patients noted additional weight loss at 1 year postoperatively, with postprandial fullness, diarrhea, and dumping symptoms (20). In our study, 76% of the patients in the surgery group had body weight loss because of these reasons. However, in the chemoradiotherapy group, only 31% of the patients had body weight loss. These results support the possibility that definitive chemoradiotherapy may become one of the standard treatments for resectable esophageal cancer.

Additionally, we examined the clinical backgrounds and biologic markers using pretreatment biopsy specimens by immunohistochemical staining to identify a better treatment for each individual. According to N stage, the Stage N1 patients treated with chemoradiotherapy had a tendency to survive longer than Stage N1 patients undergoing surgery, and the reverse phenomenon was observed for Stage N0. Many reports have indicated that lymph node metastasis is an independent poor prognostic factor in patients treated with surgery including radical node dissection (1, 21, 22). In contrast, chemoradiotherapy in this study seems to have had an equal antitumor effect and survival in patients with or without lymph node metastasis. Patients with EGFR positivity, cyclin D1 positivity, and high MVD tumors showed a very low relative risk in multivariate analysis, which favored chemoradiotherapy for survival. Because of the limitations of using a small number of subjects, our data showed no statistical significance. Additional studies, including prospective ones, are needed to confirm the usefulness of these biologic markers.

CONCLUSION

This retrospective, nonrandomized study showed a trend for better outcome after chemoradiotherapy in the treatment of squamous cell carcinoma of the esophagus. Although confirmative studies in randomized trials are needed, this trial, designed as surgical vs. nonsurgical, was hard to conduct because of difficulties in acquiring informed consent. In this circumstance, stratifying the different modalities for suitable patients by using baseline clinical and biologic markers may be a useful approach.

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SPECIAL ARTICLE

Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002

Elizabeth Horstmann, B.A., Mary S. McCabe, R.N., M.A., Louise Grochow, M.D., Seiichiro Yamamoto, Ph.D., Larry Rubinstein, Ph.D., Troy Budd, Dale Shoemaker, Ph.D., Ezekiel J. Emanuel, M.D., Ph.D., and Christine Grady, R.N., Ph.D.

ABSTRACT

BACKGROUND

Previous reviews of phase 1 oncology trials reported a rate of response to treatment of 4 to 6 percent and a toxicity-related death rate of 0.5 percent. These results may not reflect the rates in current phase 1 oncology trials.

METHODS

We reviewed all nonpediatric phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program at the National Cancer Institute between 1991 and 2002. We report the rates of response to treatment, of stable disease, of grade 4 toxic events, and of treatment-related deaths.

RESULTS

We analyzed 460 trials involving 11,935 participants, all of whom were assessed for toxicity and 10,402 of whom were assessed for a response to therapy. The overall response rate (i.e., for both complete and partial responses) was 10.6 percent, with considerable variation among trials. "Classic" phase 1 trials of single investigational chemotherapeutic agents represented only 20 percent of the trials and had a response rate of 4.4 percent. Studies that included at least one anticancer agent approved by the Food and Drug Administration constituted 46.3 percent of the trials and had a response rate of 17.8. An additional 34.1 percent of participants had stable disease or a less-than-partial response. The overall rate of death due to toxic events was 0.49 percent. Of 3465 participants for whom data on patient-specific grade 4 toxic events were available, 14.3 percent had had at least one episode of grade 4 toxic events.

CONCLUSIONS

Overall response rates among phase 1 oncology trials are higher than previously reported, although they have not changed for classic phase 1 trials, and toxicity-related death rates have remained stable. Rates of response and toxicity vary, however, among the various types of phase 1 oncology trials.

From the Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Md. (E.H., E.J.E., C.G.); the Memorial Sloan-Kettering Cancer Center, New York (M.S.M.); the Cancer Therapy Evaluation Program, National Cancer Institute, National Institutes of Health, Rockville, Md. (L.G., S.Y., L.R., T.B., D.S.); and the Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo (S.Y.) Address reprint requests to Dr. Grady at the Warren G. Magnuson Clinical Center, Bldg. 10, Rm. 1C118, National Institutes of Health, Bethesda, MD 20892-1156, or at cgrady@nih.gov.

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THE ETHICAL ISSUES RAISED BY PHASE 1 oncology trials have been debated for decades.[1-6] These trials enroll patients with advanced cancer whose disease is usually refractory to available treatment in order to evaluate the safety and toxicity of new therapeutic agents, to establish the pharmacokinetic properties of those agents, and to determine a safe dose for subsequent testing.[7] Published reviews report that a tumor response occurs in 4 to 6 percent of the participants in these trials and that about 0.5 percent of participants die as the result of toxicity.[8-16] Critics of such trials cite these data when raising concerns about the poor prospect of benefit and the potential for severe harm. Some contend that the enrollment of patients with advanced disease in risky research studies with little chance of direct benefit exploits a vulnerable population.[17] The response rates of 4 to 6 percent and the toxicity-related death rate of 0.5 percent continue to be viewed as representative of phase 1 oncology trials, but these rates are based on reviews of single-agent trials. They do not take into full account the development of new types of anticancer agents, trials of combinations of agents, new trial designs, or improvements in supportive care, and they do not present a comprehensive picture of the benefits and risks associated with phase 1 trials.[18-20]

To better inform the discussion of the risks and benefits involved in phase 1 oncology trials, we reviewed studies that began between 1991 and 2002 and were sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute, the major sponsor of phase 1 oncology trials in the United States. Reflecting the full spectrum of phase 1 oncology trials, our review included trials of chemotherapeutic agents and newer, targeted agents such as antiangiogenesis factors, vaccines, and gene therapies; trials of combinations of agents, including some already approved by the Food and Drug Administration (FDA); and published and unpublished trials. To extend our understanding of the benefits and risks associated with phase 1 oncology research, data on stable disease and grade 4 toxic events are reported in addition to conventional measures of outcome.

METHODS

All nonpediatric phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program that began between 1991 and 2002 were eligible for this review, including trials that evaluated solid tumors and hematologic cancers and trials conducted at the National Institutes of Health (NIH) Clinical Center and other institutions around the United States. Excluded were phase 1–phase 2 trials, trials of radiation therapy alone, of stem-cell or bone marrow transplantation, of supportive care without anticancer agents, and of therapies for diseases other than cancer (e.g., human immunodeficiency virus disease).

The staff of the Cancer Therapy Evaluation Program plan, review, coordinate, and oversee clinical trials of investigational anticancer agents.[21] The program receives comprehensive trial data at regular intervals from investigators and actively monitors all trials through routine data submission and periodic audits. Between 1991 and 2002, data from phase 1 trials sponsored by the Cancer Therapy Evaluation Program were monitored by five different sources: the Clinical Trials Monitoring System, the Clinical Data Update System, the Annual Update System, the Quarterly Data Update, and Study Summary reports.

The Clinical Trials Monitoring System, which has been managed for the Cancer Therapy Evaluation Program by Theradex since 1979, is a database of electronically submitted case-report forms for first trials of agents in humans as well as trials of combinations of investigational new drugs and at least one FDA-approved drug that may be associated with a risk of overlapping toxic effects. Extensive data are submitted every two weeks for quality control and are maintained in a relational KnowledgeMan database (Micro Data Base Systems). Each participating institution is audited for quality assurance three times a year.

The Clinical Data Update System, managed by Capital Technology Information Systems, has received electronic data according to course of therapy and according to patient every three months since 1998. The Clinical Data Update System is generally used for late phase 1 trials of agents whose toxicity profile has been established in earlier studies. Data are maintained in a relational Oracle database. Before 1998, summary data for these trials were submitted as paper reports yearly (by the Annual Update System or by Study Summary reports), quarterly (by Quarterly Data Update), or twice a year in printed trial summaries prepared by the cooperative groups. For trials monitored by the Clinical Data Update System, the Annual Update System, Study Summary reports, and Quarterly Data Update,

each institution is audited every three years. Auditors examine the consistency of reporting, including references to source documents concerning toxic events among subjects and assessments of responses. Data reported in this article include selected variables from the database of the Cancer Therapy Evaluation Program and combine data from the program's five monitoring sources. A subgroup of 110 trials, primarily those monitored by the Annual Update System, was excluded because complete data in regard to toxicity were unavailable. None of the excluded trials were from the Clinical Trials Monitoring System's database of studies involving agents used for the first time in humans, studies involving agents filed as investigational new drugs with the FDA, or other early phase studies. The Cancer Therapy Evaluation Program provided the data on May 16, 2003.

Trials were grouped by an experienced investigator of phase 1 trials into one of six categories according to the mechanism of action of the agent or agents under investigation: cytotoxic chemotherapeutic agents, immunomodulators, receptor-transduction or signal-transduction agents (including those affecting gene reexpression), antiangiogenesis agents, gene-transfer agents, and vaccines. Each of these categories was further subdivided into four types of trials: those for single investigational agents, for multiple investigational agents, for both investigational and FDA-approved agents, and for only those agents approved by the FDA. Trials involving multiple investigational agents with different mechanisms of action were grouped according to the agent predicted to be the most toxic. Thus, any trial involving a combination of therapies that included a chemotherapeutic investigational agent was coded as a chemotherapy trial, and any trial that included an immunomodulating investigational agent but no chemotherapeutic agents was categorized as an immunomodulator trial. Trials that included both investigational and FDA-approved agents were categorized according to the mechanism of action of the investigational agent. For purposes of classification, radiation was considered an FDA-approved agent.

In cases in which the study title identified a specific disease, the study was considered disease-specific. Studies of single investigational cytotoxic chemotherapeutic agents were labeled "classic" phase 1 trials. Studies of agents being used in humans for the first time were selected from all five databases. These included the very first study of an agent conducted after the agent was filed as an investigational new drug with the FDA and trials that were initiated within seven months of the first study, before any information was available about dose-limiting toxicity from the very first trial.

Potentially beneficial effects of agents under investigation were categorized as complete response, partial response, less-than-partial response, and stable disease. Response to treatment was reported for each protocol according to guidelines of the World Health Organization (WHO),[22] the Response Evaluation Criteria in Solid Tumors,[23] or other established criteria approved by the Protocol Review Committee of the Cancer Therapy Evaluation Program. A complete response was defined as the disappearance of a tumor; a partial response as an overall 50 percent reduction in the tumor, measured as the sum of the products of the two longest diameters (according to the WHO criteria), or as an overall 30 percent reduction in tumor size, measured as the sum of the longest diameters (according to guidelines of the Response Criteria in Solid Tumors); and stable disease as neither a partial response nor progressive disease.[23] For this analysis, less-than-partial response and stable disease are combined into one category.

Toxicity was reported with the use of the Common Toxicity Criteria.[24] Protocols specified which version of these criteria were used, depending on when the protocols were initiated. All deaths reported by investigators as "possibly," "probably," or "definitely" related to treatment were considered toxicity-related deaths. Data on patient-specific grade 4 toxic events that were available from the Clinical Data Update System are reported; for the other trials, only the data on cumulative toxicity according to trial were available.

STATISTICAL ANALYSIS

Response rates, death rates, and rates of grade 4 toxic events were calculated for participants who were assessed according to trial category (i.e., therapeutic modality, single agent or combination, disease-specific or not, and first-in-human or other). Rates were calculated by dividing the total number of events (responses, deaths, or grade 4 toxic events) by the total number of patients assessed for response or toxicity. Response rates and toxicity-related death rates were also calculated for three-year intervals to evaluate trends. For the subgroup of trials monitored by the Clinical Data Update System, the percentage of patients who had grade 4

toxic events and the average number of grade 4 toxic events per affected patient were reported. Comparisons of response rates and of toxicity-related death rates — in particular, between the current sample and prior samples — were made descriptively. Calculation of statistical significance was intentionally avoided in cases where patient samples may have been divergent and hypothesis testing not prospectively defined. Statistical analyses were performed with the use of SAS software, version 8.02.

RESULTS

The sample of 460 phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program

Table 1. Rates of Response to Treatment in Phase 1 Oncology Trials.

Trial	No. of Trials	No. of Patients Assessed for Response	Rate of Response			
			Overall Response (Complete and Partial)	Complete Response	Partial Response	Stable Disease and Less-Than-Partial Response
				percent		
Total	460	10,402	10.6	3.1	7.5	34.1*
Cytotoxic chemotherapy						
One investigational agent	92	2,341	4.4	1.5	2.9	40.8
Multiple investigational agents	12	273	11.7	1.5	10.3	27.5
Combination of investigational and FDA-approved agents	88	2,251	16.4	5.6	10.8	31.3†
FDA-approved agents only	29	792	27.4	8.0	19.4	27.2†
Immunomodulator						
One investigational agent	13	203	11.3	3.0	8.4	35.5
Multiple investigational agents	28	651	6.9	2.2	4.8	22.3†
Combination of investigational and FDA-approved agents	19	392	26.0	5.6	20.4	26.7†
Receptor or signal transduction						
One investigational agent	51	1,347	3.2	0.7	2.5	39.3
Multiple investigational agents	7	81	7.4	1.2	6.2	27.2
Combination of investigational and FDA-approved agents	61	935	11.7	2.1	9.5	37.4
Antiangiogenesis						
One investigational agent	15	335	3.9	0.6	3.3	31.0
Combination of investigational and FDA-approved agents	9	135	14.8	5.2	9.6	37.0
Gene transfer						
One investigational agent	7	89	3.4	0	3.4	30.3
Combination of investigational and FDA-approved agents	1	3	0	0	0	0
Vaccine						
One investigational agent	15	265	3.4	3.0	0.4	24.9
Multiple investigational agents	7	198	1.0	1.0	0	35.4
Combination of investigational and FDA-approved agents	6	111	5.4	2.7	2.7	19.8

* For 630 of 10,402 participants, data on stable disease and less-than-partial response are not reported. The percentage was calculated with 9772 as the denominator.

† Percentages were calculated with a denominator adjusted to exclude participants for whom data on stable disease and less-than-partial response were unavailable.

that opened between 1991 and 2002 included 11,935 participants. All participants were assessed for toxicity, and 10,402 were assessed for a response (Table 1). Trials of cytotoxic chemotherapeutic agents accounted for 48.0 percent (221) of all trials and for 54.4 percent (5657) of participants assessed for response. Trials involving receptor transduction or signal transduction were the second-largest group (119 trials, or 25.9 percent), representing 22.7 percent (2363) of participants assessed for response. There were only eight trials involving gene transfer, with 92 participants (Table 1).

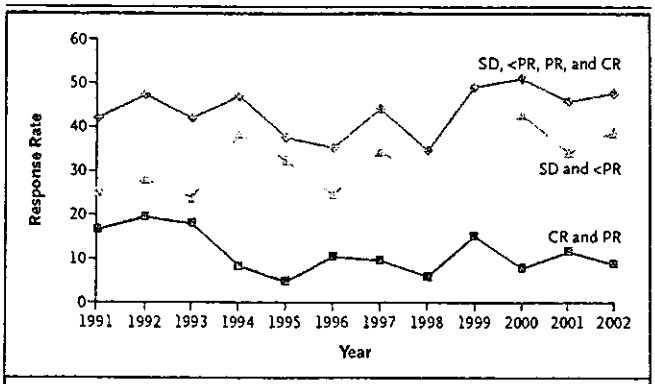

Figure 1. Response Rates According to Year.

Response to therapy was classified as complete (CR), partial (PR), less than partial (<PR), or as stable disease (SD). When the rates were grouped according to three-year periods, a downward trend was observed for complete and partial responses, but when stable disease and less-than-partial responses were taken into account, the rate remained relatively constant over time.

RESPONSE RATES

Among the trials of all types of agents, 10.6 percent of the 10,402 participants assessed for response had either a partial or a complete response to therapy. Of these, 7.5 percent had a partial response and 3.1 percent had a complete response. In addition, 34.1 percent of the participants in phase 1 trials had either stable disease or a less-than-partial response (Table 1).

Response rates varied according to the type of agent used and the characteristics of the trial (Table 1). The overall response rate was 3.0 percent among trials of vaccines and 13.6 percent among studies of immunomodulators (data not shown). Furthermore, response rates varied within categories according to the type of trial. For classic phase 1, single-agent chemotherapy studies, the overall response rate was 4.4 percent. The rate among chemotherapy studies involving more than one investigational agent was 11.7 percent; for combinations of investigational and FDA-approved agents, the rate was 16.4 percent; and for phase 1 trials including only FDA-approved chemotherapeutic agents, the rate was 27.4 percent (Table 1). A similar variation was seen in the other categories of trials (Table 1). The response rate among 3420 participants in 184 disease-specific trials was 19.3 percent; among trials that were not specific to disease, the rate was 6.3 percent.

Response rates also varied over time, with the highest rate (19.5 percent) occurring in 1992 and the lowest (5.0 percent) in 1995. When the rates were grouped according to three-year periods, a downward trend in complete and partial responses was noted (18.3 percent for 1991 to 1993 and 9.4 percent for 2000 to 2002). However, when stable disease was taken into account, the rate remained relatively constant over time (34.6 to 51.3 percent) (Fig. 1).

TOXICITY

Among the 11,935 participants in all 460 phase 1 studies, there were 58 deaths (0.49 percent) that were determined to be at least possibly related to the treatment (Table 2). Of those deaths, 18 were reported as definitely related to the treatment and 7 as probably related (for a combined toxicity-related death rate of 0.21 percent). When calculated in three-year intervals for 1991 through 2002, the toxicity-related death rate remained relatively constant (range, 0.45 to 0.61 percent). Of the 58 deaths, 43 (74.1 percent) occurred in participants in chemotherapy trials, with the highest toxicity-related death rate (0.77 percent) occurring in trials involving both investigational and FDA-approved agents (Table 2). Classic phase 1 trials of single investigational chemotherapeutic agents had a toxicity-related death rate of 0.57 percent. Thirteen deaths were reported among trials of receptor-transduction or signal-transduction agents (0.47 percent) and one death each among trials of immunomodulators (0.07 percent) and antiangiogenesis factors (0.17 percent). There were no reported deaths in phase 1 gene-transfer or vaccine studies.

In a subgroup of 168 studies that involved 3465 patients assessed for toxicity, 14.3 percent of participants had had grade 4 toxic events; an average of 1.9 grade 4 events occurred per affected patient (Table 3). On average, trials of chemotherapeutic agents were associated with the highest rate of tox-

Table 2. Deaths from Toxic Events in Phase 1 Oncology Trials.

Trial	No. of Trials	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events*
			no. (%)
Total	460	11,935	58 (0.49)
Cytotoxic chemotherapy			
One investigational agent	92	2,621	15 (0.57)
Multiple investigational agents	12	305	2 (0.66)
Combination of investigational and FDA-approved agents	88	2,594	20 (0.77)
FDA-approved agents only	29	925	6 (0.65)
Immunomodulator			
One investigational agent	13	235	0
Multiple investigational agents	28	730	1 (0.14)
Combination of investigational and FDA-approved agents	19	443	0
Receptor or signal transduction			
One investigational agent	51	1,565	3 (0.19)
Multiple investigational agents	7	99	2 (2.02)
Combination of investigational and FDA-approved agents	61	1,081	8 (0.74)
Antiangiogenesis			
One investigational agent	15	402	0
Combination of investigational and FDA-approved agents	9	171	1 (0.58)
Gene transfer			
One investigational agent	7	107	0
Combination of investigational and FDA-approved agents	1	5	0
Vaccine			
One investigational agent	15	297	0
Multiple investigational agents	7	218	0
Combination of investigational and FDA-approved agents	6	137	0

* Deaths include all those reported as possibly, probably, or definitely related to the treatment.

icity, with 17.4 percent of participants experiencing at least one grade 4 toxic event; vaccine trials had the lowest rate, with no grade 4 toxic events reported (Table 3). Among all 11,935 participants assessed in the 460 studies, 5251 grade 4 toxic events were reported.

FIRST-IN-HUMAN TRIALS

Of 460 trials, 117 (25.4 percent) involving a total of 3164 participants assessed for a response to therapy were considered first-in-human trials — that is, studies designed to establish initial information on toxicity and dose for agents not previously tested in humans (Table 4). The overall response rate in these studies was 4.8 percent, as compared with 13.1 percent in the other studies. The toxicity-related death rate in first-in-human studies was 0.26 percent, as compared with 0.58 percent in studies not considered first-in-human trials. Studies of cytotoxic chemotherapeutic agents made up the largest group of first-in-human trials (36.8 percent). Of the vaccine studies sponsored by the Cancer Therapy Evaluation Program, 82.1 percent were first-in-human trials.

Table 3. Grade 4 Toxic Events in Phase 1 Oncology Trials.

Trial	No. of Trials	No. of Patients Assessed for Toxic Events	Patients with a Grade 4 Toxic Event	Average No. of Grade 4 Toxic Events per Patient
			%	
Total	168	3465	14.3	1.9
Cytotoxic chemotherapy				
One investigational agent	20	408	15.0	1.6
Multiple investigational agents	3	23	4.3	2.0
Combination of investigational and FDA-approved agents	17	475	14.5	1.8
FDA-approved agents only	3	159	34.0	2.4
Immunomodulator				
One investigational agent	2	43	2.3	1.0
Multiple investigational agents	10	207	9.7	2.2
Combination of investigational and FDA-approved agents	5	101	4.0	1.8
Receptor or signal transduction				
One investigational agent	29	839	13.0	1.7
Multiple investigational agents	6	67	19.4	2.0
Combination of investigational and FDA-approved agents	51	752	18.1	2.0
Antiangiogenesis				
One investigational agent	9	143	5.6	1.6
Combination of investigational and FDA-approved agents	6	101	17.8	1.8
Gene transfer				
One investigational agent	1	26	11.5	1.7
Combination of investigational and FDA-approved agents	1	5	0	0
Vaccine				
One investigational agent	3	20	0	0
Multiple investigational agents	2	96	0	0

TRIALS WITH FDA-APPROVED AGENTS

Overall, 213 studies (46.3 percent) included at least one FDA-approved anticancer agent. Response rates were higher in trials with FDA-approved agents than in trials without FDA-approved agents (Table 5). These studies had an overall response rate of 17.8 percent, as compared with 4.8 percent for studies not including FDA-approved anticancer agents. The toxicity-related death rate was higher (0.65 percent) than for trials that did not include FDA-approved anticancer agents (0.35 percent).

DISCUSSION

We comprehensively reviewed phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program between 1991 and 2002. The overall response rate in these trials was 10.6 percent, which is higher than previously reported, whereas the toxicity-related death rate, 0.49 percent, is similar to that of previous reports. Rates of response and of toxicity-related death among classic phase 1 trials of single chemotherapeutic agents are similar to those reported in other reviews, but classic trials account for only 22 percent of participants in this review.

Response rates in phase 1 oncology trials have been reported to be 4 to 6 percent, with toxicity-related death rates reported to be 0.5 percent or lower.[8-16] In our review, however, we found that response rates in recent phase 1 oncology trials exceeded 10 percent, with stable disease or less-than-partial re-

Table 4. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials Involving the First Use of an Agent in Humans.

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate*	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events†
			%		*no. (%)*
Total					
First use of an agent in humans	117	3164	4.8	3498	9 (0.26)
All other trials	343	7238	13.1	8437	49 (0.58)
Cytotoxic chemotherapy					
First use of an agent in humans	43	1298	5.0	1422	7 (0.49)
All other trials	178	4359	15.0	5023	36 (0.72)
Immunomodulator					
First use of an agent in humans	16	404	7.4	431	1 (0.23)
All other trials	44	842	16.6	977	0
Receptor or signal transduction					
First use of an agent in humans	27	742	3.8	853	1 (0.12)
All other trials	92	1621	8.0	1892	12 (0.63)
Antiangiogenesis					
First use of an agent in humans	8	200	7.0	228	0
All other trials	16	270	7.0	345	1 (0.29)
Gene transfer					
First use of an agent in humans	0	0	0	0	0
All other trials	8	92	3.3	112	0
Vaccine					
First use of an agent in humans	23	520	3.1	564	0
All other trials	5	54	1.9	88	0

* The overall response rate includes both complete and partial responses.
† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

sponse having been achieved in an additional 34.1 percent of participants. Rates of toxicity-related death have not increased over time, and more than 85 percent of participants had no grade 4 toxic events. As compared with other reviews, these data suggest that participants may benefit more from current phase 1 oncology trials than previously believed.

A recent review of single-agent trials showed that there was a decrease in tumor-response rates over time,[13] which was attributed to the use of newer, more specific agents and changes in trial design. In our review, response rates per year varied without a clear pattern. When these rates were grouped in three-year intervals, there was a decrease in complete or partial responses from 1991 to 2002 but an increase in rates of stable disease. Little change in the benefit to participants over time was seen when response rates were grouped with stable disease.

In our view, it is inaccurate to refer to phase 1 oncology studies as if they are all similar to one another. Nearly half of the trials we studied included at least one FDA-approved agent, and less than half included chemotherapeutic agents. Different types of phase 1 oncology studies are associated with very different response rates. For instance, the response rate among patients who were treated with immunomodulators was 13.6 percent, yet the rate was just 3.0 percent for patients treated with vaccines. Trials that included one or more FDA-approved anticancer agents showed higher response rates than did those involving only investigational agents. For these reasons, it may be misleading to summarize phase 1 oncology trials with the use of a single response rate.

Risk, as measured by toxicity-related death rates and grade 4 toxic events, also varies according to the type of trial. The average toxicity-related death rate for trials of cytotoxic chemotherapeutic agents was 0.67 percent but just 0.07 percent for those in-

Table 5. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials, According to Whether FDA-Approved Agents Were Used.

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate*	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events†
			%		*no. (%)*
Single investigational agent	193	4580	4.2	5227	18 (0.34)
Multiple investigational agents	54	1203	7.1	1352	5 (0.37)
Combination of investigational and FDA-approved agents	184	3827	15.8	4431	29 (0.65)
FDA-approved agents only	29	792	27.4	925	6 (0.65)

* The overall response rate includes both complete and partial responses.
† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

volving immunomodulators, and no toxicity-related deaths were reported in gene-transfer or vaccine trials. Grade 4 toxic events were more common in chemotherapy trials, especially those involving multiple agents, than in all other trials. Trials of FDA-approved drugs, which evaluated the safety of higher doses or combinations of drugs, appeared to be associated with the highest rates of toxicity (a death rate from toxic events of 0.65 percent, vs. 0.35 percent for other trials) but also had the highest overall response rate (17.8 percent, vs. 4.8 percent for other trials). Overall, newer, nonchemotherapeutic agents are associated with lower rates of toxic events.

Classic phase 1 studies of single investigational chemotherapeutic agents, which were the only trials included in previous reviews, showed an overall response rate of 4.4 percent and a toxicity-related death rate of 0.57 percent. These rates are almost identical to those previously reported.[8-16] In this study of trials sponsored by the Cancer Therapy Evaluation Program and initiated between 1991 and 2002, classic phase 1 trials accounted for only 22 percent of all participants. Similarly, the testing of investigational agents never before studied in humans is commonly thought of as a defining characteristic of phase 1 oncology trials. In our review, these first-in-human studies represented less than a quarter of phase 1 studies and enrolled less than a third of participants. Response rates, but also toxicity-related death rates, are lower in studies that test agents for the first time in humans than in those that do not test agents for the first time.

When the risks and benefits associated with phase 1 oncology trials are weighed, factors other than response rates and toxicity should be taken into account. Investigational treatments may have clinically meaningful benefits — reduced pain, increased appetite, energy, and activity, weight gain, reduced fatigue, or increased ability to perform daily activities.[20,25,26] Some of these benefits might accrue from research participation itself; for some persons, contributing to research and potentially helping future cancer patients may also be an important benefit.[27] At the same time, participation in research may involve additional burdens: multiple visits or long hours at the clinic, unpleasant procedures, and the possible financial costs associated with participation in research studies.[28]

This study has several limitations. First, our data are derived only from trials sponsored by the Cancer Therapy Evaluation Program. Although the program is a major sponsor of phase 1 oncology trials in the United States[29] and the use of data from the program avoids publication bias, any differences that might be found in the phase 1 trials with other sponsors have not been captured. It is possible that the response rates associated with trials of promising agents sponsored by pharmaceutical companies could be higher than those reported here. Second, for trials involving gene transfer, the findings should be interpreted with caution because of the small number of trials and the possibility that outliers influenced the data. Finally, our reporting of grade 4 toxic events is limited. Patient-specific data on grade 4 toxic events came from one monitoring source, which, although it includes some first-in-human trials, is generally used to monitor later phase 1 studies and may not be entirely representative of phase 1 oncology studies. Moreover, the data on grade 4 toxic events are reported without distinguishing among the types of toxic events.

Since not all toxic events have similar medical consequences, evaluation of the risks in phase 1 trials should include both the types and the frequency of events experienced by participants.

In conclusion, reliance on a single estimate of the response rate or the toxicity-related death rate for phase 1 oncology trials is misleading, since rates of response and toxicity vary according to the type of trial. Potential participants and their families, oncologists, investigators, members of institutional review boards, ethicists, and others interested in weighing the risks and benefits of phase 1 studies and making decisions about their acceptability should be aware of the complexity and variety of such trials, know the details about the trial they are considering, and carefully evaluate all relevant risks and benefits.

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Demographics, lifestyles, health characteristics, and dietary intake among dietary supplement users in Japan

Junko Ishihara,[1] Tomotaka Sobue,[1] Seiichiro Yamamoto,[1] Satoshi Sasaki,[2,3] and Shoichiro Tsugane[2] for the JPHC Study Group[4]

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Background The associations between supplement use and certain demographics, lifestyles, health characteristics, and dietary intakes have not been studied in a large population in non-Western societies. The objective of our study was to investigate the association between supplement use and demographics, lifestyles, health characteristics, and dietary intake in a population-based cohort study in Japan.

Methods Subjects were the 78 531 participants (45–74 years) who completed a self-administered questionnaire in 1995 or 1998 in a 5-year follow-up survey by the Japan Public Health Center-based prospective Study on cancer and cardiovascular disease. The questionnaire included enquiries about supplement use, occupation, height, weight, smoking, alcohol, physical activity, dietary behaviours, working hours, subjective stress, as well as intakes for 138 foods.

Results The supplement users were likely to have formerly smoked or never smoked. Female supplement users were likely to consume alcohol moderately. The prevalence of users was higher in the elderly, the self-employed, those with lower body mass index, greater physical activity, lower frequency of eating prepared food, higher frequency of eating out, and higher stress level in both sexes after mutual adjustment. Mean intakes of energy and nutrients were lower for users than for non-users.

Conclusion The demographics, lifestyles, health characteristics, and dietary intakes may need to be adjusted when evaluating the effect of dietary supplements on disease because they can become potential confounding factors.

Keywords Dietary supplements, characteristics, cohort study

Commercially available dietary supplements in Japan have seen tremendous growth over the last decade,[1] and their variety and number continue to increase. The prevalence of dietary supplement users differs depending on the study population as well as the definition of supplements and survey methods used. In the US, where dietary supplements are generally very popular, the prevalence varied from 21% to 55% among a number of different studies.[2] In our previous report for the baseline survey by the Japan Public Health Center-based prospective Study on cancer and cardiovascular disease (JPHC Study) in 1990 and 1993, the users who took vitamin supplements ≥1 week ranged from 4.4% to 22.7% by area.[3]

In epidemiological studies, the use of dietary supplements is an exposure of interest because of its potential effect on disease. When dietary supplement use is associated with both diseases and demographic factors such as sex, age, race, and socio-economic status,[4] and health-related characteristics such as body mass index (BMI), smoking, and alcohol consumption,[5–7] as well as certain psychological factors,[8] it also becomes a confounding factor when determining other risk factors. These

[1] Cancer Information and Epidemiology Division, National Cancer Center Research Institute, Tokyo, Japan.
[2] Epidemiology and Biostatistics Division, National Cancer Center Research Institute East, Kashiwa, Japan.
[3] Current affiliation: National Institute of Health and Nutrition, Tokyo, Japan.
Correspondence: Junko Ishihara, Cancer Information and Epidemiology Division, National Cancer Center Research Institute, 5–1–1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: junishih@gan2.ncc.go.jp

associations have been investigated extensively in Western countries where supplements have been widely used for decades. However, little is known about the characteristics of dietary supplement users in non-Western countries, including Japan.

In this report, we aimed to determine the characteristics of dietary supplement users among the participants in the JPHC Study cross-sectionally. The objective of our study was to investigate the possible association between supplement use and demographics, lifestyles, health characteristics, and dietary intakes.

Materials and Methods

Subjects

The study population of the JPHC Study were 140 420 adults (29 982 males and 31 613 females in Cohort I, and 38 740 males and 40 085 females in Cohort II) from 11 Public Health Center (PHC) areas in Japan. Cohort I started in 1990 with population-based cohorts of all 40–59 year old residents of four PHC areas (Yokote, Ninohe, Saku, and Ishikawa), together with a health check-up cohort in which all 40 and 50 year old residents of a PHC area (Katsushika) were invited to participate. Cohort II started in 1993 with population-based cohorts of all 40–69 year old residents of five PHC areas (Mito, Kashiwazaki, Chuo-higashi, Kamigoto, and Miyako), together with two health check-up cohorts (Suita 1 and Suita 2). Suita 1 comprised 40 and 50 year old residents of Suita City who participated in a comprehensive municipal health check-up programme. Suita 2 comprised 40–69 year old participants from the Suita Study, in which the participants were randomly selected from all 30–79 year old residents of Suita based on the population registry. The locations of study sites are shown in Figure 1. Study sites of the JPHC Study encompass the prefectures with the lowest and highest mortality rates. They were distributed throughout Japan and consisted of both urban and rural communities.[9] Katsushika and Suita are urban areas located in two major cities in Japan where a large proportion of subjects were engaged with manufacturing, trade, and service sectors. Other areas were rather rural, where farming and fishing were prominent. Baseline surveys were conducted in each cohort at the beginning of the study. Details on the selection of cohort participants and the baseline survey were presented elsewhere.[10]

Data collection

We conducted a 5-year follow-up survey from the baseline in 1995 for Cohort I, and in 1998 for Cohort II. A food frequency questionnaire (FFQ) was collected from 103 769 subjects (45 019 for Cohort I, 58 750 for Cohort II). The response rates ranged from 77% to 90% in all areas except for the metropolitan areas Katsushika (40%), Suita 1 (43%), and Suita 2 (60%), and Ishikawa (63%). This FFQ with 138 food items had been developed to estimate dietary intake,[11] and validated for estimations of various nutrients and food groups.[12–14] It also included questions about dietary supplement use as well as demographics, lifestyles, and health characteristics such as occupation, height, weight, smoking, alcohol consumption, physical activity, dietary behaviours, working hours, and stress.

In the FFQ, general use of any vitamin supplements more than once a week, and use of specific supplements by five categories (Multivitamin, Beta-carotene, Vitamin C, Vitamin E, Others) were probed. For each category, the brand names, frequency, and duration of use were asked. Users of dietary supplements were defined as subjects who used at least one category of dietary supplement $\geq$1 week for $\geq$1 year. If a subject was a user of at least one category of supplement, he or she was regarded as an overall supplement user. To preclude the incorrect categorization of self-reported dietary supplements, all supplements in the FFQ were re-categorized by the authors using brand names according to the definition of dietary supplements in the Women's Healthy Eating and Living Study.[15] This method of defining the supplement users was validated in our previous study.[16] Recategorizing self-reported categories was shown to improve sensitivity in identifying dietary supplement users. The results from our validation study also indicated that our questionnaire could even identify non-vitamin supplement users to a certain extent (sensitivity of 75%), although we only enquired about vitamin supplement use.

Self-reported occupations were combined into the following six groups: farming, forestry, and fishing; employee and professional; housewife; self-employed; unemployed; and other occupations. The subjects with $\geq$2 occupations across those groups were classified as a combination group. Body mass index for each subject was computed based on self-reported height and weight by dividing weight (kg) by the square of height (m). The questionnaire covered smoking status, frequency of alcohol consumption, physical activity, 14 questions on dietary behaviours (frequency of eating miso soup, breakfast, eating out, consumption of prepared foods, fried foods, deep-fried foods, fat on meat, soup from noodle bowls, adding salt or soy sauce to foods at the table, types of vegetable oils used, frequently used cooking methods, well-doneness of cooked meat, eating charred parts of fish), working hours, and self-reported stress.

Individual intakes of energy and 33 nutrients were calculated from 138 food items in the FFQ. The algorithm of the calculation was reported elsewhere.[17] Intake from dietary supplements was not included in that calculation.

Statistical analysis

SAS version 8.02 (SAS Institute Inc., Cary, NC) was used to conduct all the statistical analyses. We excluded subjects who were confirmed to be ineligible during the follow-up because they were not Japanese nationals, had already moved away at the baseline, or were not in the intended age group for this study. Subjects were also excluded for the following reasons: BMI of $<$10 or $>$100; failure to supply data in the questionnaire for any of the variables used such as occupation, height, weight, smoking, alcohol consumption, physical activity, dietary behaviours, working hours, and stress; men with a total energy intake of $<$900 kcal or $\geq$4000 kcal; women with a total energy intake of $<$800 kcal, or $\geq$3600 kcal. Of 103 769 subjects who completed the questionnaire, a total of 78 531 subjects (37 298 men and 41 233 women) were finally included in the analysis. The proportion of demographic, lifestyle, health characteristics, and supplement use among those who were excluded was similar to those included in the analysis.

We calculated the prevalence of dietary supplement users for each of the demographic factors, lifestyles, and health

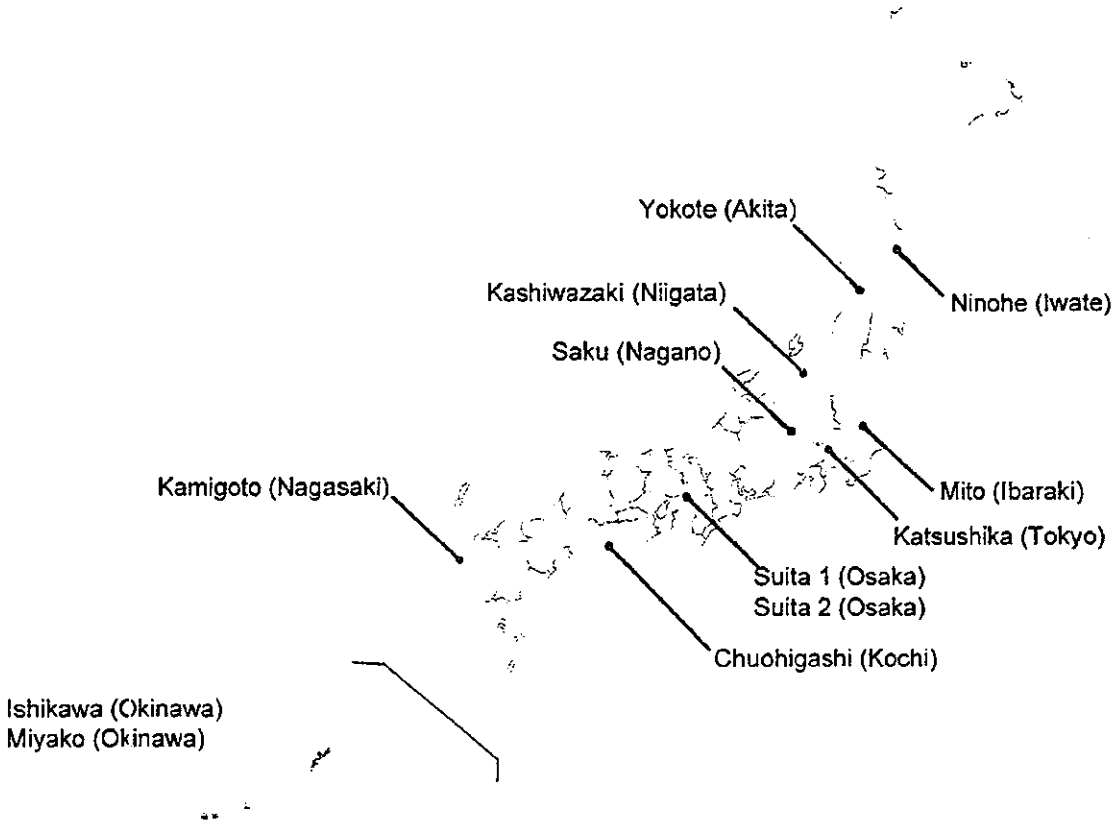

Figure 1 Study sites of the Japan Public Health Center-based prospective study on cancer and cardiovascular disease

characteristics by sex. The odds ratios (OR) with 95% CI were computed using a logistic regression model for the association between dietary supplement use and those factors. *P*-values for linear trends from the lowest to the highest levels of each variable were calculated using logistic regression.

Individual intakes of energy and nutrients were transformed using the natural log scale to normalize skewed distribution. Energy intake was adjusted for area, age group, occupation, smoking, alcohol consumption, physical activity, dietary behaviour, working hours, and stress level using LSMEANS of PROC GLM in SAS. Nutrient intakes were adjusted for the same variables and for energy intake using the same procedure. The geometric means of energy and nutrient intakes by sex were calculated for users and non-users of dietary supplements by the back-transformation of least-square means. The percentage difference was also calculated by dividing the difference in mean intakes between user and non-user by the mean intake of users.

Results

The percentage of dietary supplement users and OR in relation to the reference group by demographics, lifestyles, and health characteristics was shown in Table 1. Among the 12 areas of the JPHC Study, the prevalence was high in urban areas (Katsushika and Suita) and in mainland Okinawa (Ishikawa). Among the 5-year age groups, the prevalence of dietary supplements was lowest in the youngest group, 45–49 years. There was a significant linear increase in dietary supplement users among the higher age groups.

Among the six occupation groups, the self-employed were most likely, and the farming, forestry, and fishing group members were least likely to be supplement users after the adjustment. As for smoking, prevalence of users was significantly lower for current smokers in men, whereas it was significantly higher for former smokers in women. A difference in prevalence by the frequency of alcohol consumption was observed only in women. Women who drank moderately (once a month to 6 times a week) were most likely to be users. For BMI, there was a significant linear decrease of dietary supplement users for higher BMI groups in both sexes. Regarding exercise, there was a significant linear increase in those groups who exercise more frequently.

In the initial analysis of 14 dietary behaviours and the use of dietary supplements, no association was observed with the frequency of eating breakfast, consumption of fried foods, deep-fried foods, and fat on meat, of eating soup from noodle bowls, adding salt or soy sauce to foods at the table, types of vegetable oils used, frequently used cooking methods, well-doneness of cooked meat, and eating charred parts of fish (data not shown). Therefore, we included in the logistic model the only three variables as dietary habits associated with supplement use (frequency of eating miso soup, consumption of prepared foods

Table 1 Percentage of people in the 5-year follow-up survey in Japan Public Health Center-based prospective study on cancer and cardiovascular disease with indicated demographics, lifestyles, and health characteristics of subjects who used dietary supplements

	Male						Female					
	n	User (%)	Odds ratio[a]	95% CI		P-value[b]	n	User (%)	Odds ratio[a]	95% CI		P-value[b]
Area						–						–
Ninohe	3683	5.6	0.59	0.50	0.70		4362	10.0	0.81	0.72	0.92	
Yokote	5063	10.4	1.09	0.96	1.23		6070	14.5	1.11	1.00	1.23	
Saku	4278	9.4	0.95	0.83	1.08		4390	12.6	0.92	0.82	1.04	
Ishikawa	2996	14.5	1.48	1.29	1.69		3134	24.2	2.12	1.89	2.37	
Katsushika	775	18.6	1.75	1.43	2.15		1178	24.9	1.71	1.46	1.99	
Mito	6792	10.8	1.00[c]				6667	14.7	1.00[c]			
Kashiwazaki	1115	8.5	0.81	0.65	1.02		1105	11.0	0.76	0.62	0.94	
Chuo-higashi	2662	11.1	1.11	0.96	1.29		2921	17.2	1.30	1.15	1.47	
Kamigoto	2979	8.8	0.95	0.81	1.11		3349	13.3	1.03	0.91	1.16	
Miyako	3793	7.4	0.72	0.62	0.84		4215	13.4	1.03	0.92	1.16	
Suita 1	1737	21.9	2.07	1.78	2.41		1954	30.6	2.19	1.92	2.49	
Suita 2	1425	24.0	2.03	1.74	2.37		1888	34.3	2.43	2.15	2.76	
Age (years)						< 0.001						< 0.001
–49	9906	9.1	1.00[c]				10 539	15.0	1.00[c]			
50–54	7151	9.4	1.17	1.05	1.31		7707	15.6	1.24	1.13	1.35	
55–59	8569	13.4	1.52	1.38	1.67		9801	19.0	1.40	1.29	1.51	
60–64	7091	11.3	1.75	1.57	1.96		7807	15.4	1.49	1.36	1.63	
65–69	2667	12.6	2.00	1.71	2.35		3014	17.5	1.71	1.51	1.94	
70–	1914	12.6	2.05	1.71	2.47		2365	17.0	1.73	1.51	1.99	
Occupation												
Farming, forestry, and fishing	6837	6.7	0.66	0.59	0.75		4948	8.6	0.56	0.50	0.63	
Employee or professional	16 225	11.8	1.00[c]				9775	17.2	1.00[c]			
Housewife	–	–	–	–	–		10 594	18.9	0.97	0.89	1.06	
Self-employed	6397	13.0	1.16	1.06	1.27		3814	21.6	1.26	1.14	1.39	
Unemployed	2269	14.1	1.04	0.87	1.24		1695	14.6	0.76	0.65	0.89	
Other occupation	2144	10.4	0.94	0.81	1.10		2299	16.6	0.92	0.81	1.04	
Combination[d]	3426	10.4	1.06	0.94	1.20		8108	14.9	0.88	0.80	0.96	
Smoking						–						–
Current	17 443	9.9	0.87	0.80	0.94		2347	19.4	1.00	0.89	1.12	
Former	6809	13.1	1.06	0.96	1.16		470	28.1	1.40	1.13	1.73	
Never	13 046	11.4	1.00[c]				38 416	16.1	1.00[c]			
Alcohol consumption						0.29						< 0.001
None	8518	10.8	1.00[c]				32 398	15.2	1.00[c]			
1/month–2/week	6299	11.4	1.07	0.96	1.20		5026	20.4	1.26	1.16	1.36	
3–6 times/week	7537	11.8	1.05	0.95	1.16		2350	22.0	1.21	1.08	1.35	
Daily	14 944	10.5	0.97	0.88	1.06		1459	21.3	1.12	0.98	1.28	
Body mass index (kg/m²)						< 0.001						< 0.001
<19	1557	12.1	1.12	0.94	1.33		2512	19.8	1.15	1.03	1.29	
19–<21	5183	11.5	1.06	0.95	1.18		6585	19.5	1.14	1.05	1.24	
21–<23	9145	11.1	1.00[c]				10 923	16.9	1.00[c]			
23–<25	10 785	11.3	1.01	0.92	1.10		9982	16.1	0.96	0.89	1.04	
25–<27	6417	10.7	0.91	0.82	1.01		6187	14.0	0.83	0.76	0.91	
27–<30	3426	9.4	0.80	0.70	0.92		3800	13.3	0.78	0.70	0.87	
≥30	785	8.8	0.75	0.58	0.97		1244	13.7	0.75	0.63	0.89	
Exercise						< 0.001						< 0.001
Never	21 709	9.5	1.00[c]				27 798	14.8	1.00[c]			
1/month–2/week	11713	12.3	1.19	1.11	1.29		9024	19.2	1.22	1.14	1.30	
3 times/week–daily	3876	15.3	1.50	1.35	1.66		4411	21.3	1.38	1.27	1.50	
Miso soup						0.58						0.32
≤2/week	4330	14.0	1.02	0.92	1.14		5508	21.4	1.03	0.95	1.12	
3–6 times/week	9366	12.4	1.03	0.95	1.11		11 426	18.6	1.04	0.98	1.11	
Daily	23 602	9.9	1.00[c]				24 299	14.3	1.00[c]			
Prepared food						< 0.05						< 0.001
Never	10 418	12.0	1.00[c]				17 118	17.0	1.00[c]			
1/month–2/week	24 453	10.6	0.91	0.85	0.98		23 172	16.1	0.91	0.86	0.96	
3 times/week–daily	2427	10.5	0.91	0.78	1.05		943	15.7	0.83	0.69	1.00	
Eating out						< 0.001						< 0.001
Never	11 795	8.1	1.00[c]				16 800	12.3	1.00[c]			
1–3 times/month	12 816	10.9	1.29	1.18	1.41		17 771	18.0	1.42	1.33	1.51	
1–2 times/week	4690	12.6	1.42	1.26	1.59		3960	23.4	1.69	1.54	1.86	
3 times/week–daily	7997	14.6	1.57	1.41	1.74		2702	21.9	1.61	1.44	1.80	

Table 1 continued

	Male						Female					
	n	User (%)	Odds ratio[a]	95% CI		P-value[b]	n	User (%)	Odds ratio[a]	95% CI		P-value[b]
Working hours						< 0.005						0.60
<5 hours	5099	12.3	1.00[c]				13 724	17.5	1.00[c]			
5–9 hours	24 124	10.3	0.97	0.85	1.11		22 668	15.5	0.93	0.87	0.99	
≥9 hours	8075	12.3	1.13	0.98	1.31		4841	17.8	1.08	0.98	1.19	
Stress level						< 0.001						< 0.001
Low	6891	10.4	1.00[c]				7690	15.3	1.00[c]			
Medium	22 886	10.3	1.06	0.97	1.16		25 941	15.5	1.08	1.00	1.16	
High	7521	13.7	1.42	1.27	1.58		7602	20.6	1.47	1.35	1.61	
Total	37 298	11.0					41 233	16.4				

[a] Variables were mutually adjusted.

[b] P-values for linear trend from the lowest to the highest group using logistic regression.

[c] Ref.

[d] Subjects with multiple occupations.

such as freeze-dried noodles and retort-pouched foods, and eating out). For miso soup, although the prevalence of dietary supplement users was highest in the subjects who consumed the least, the difference was not significant after the adjustment for other variables. For prepared foods, the prevalence of users was highest in subjects who never used them. The prevalence of users was highest in the groups with the highest frequency of eating out. There was also a significant linear increase of users in the groups of subjects who eat out more frequently.

Working hours were not associated with dietary supplement use after adjustment for other variables. For stress level, the groups reporting high stress were most likely to be users.

The geometric means of energy and nutrient intakes from diet for users and non-users of any dietary supplement and their percentage difference by sex are shown in Table 2. The mean intake was significantly lower for users as was intake of energy and most nutrients except for sodium and niacin for both sexes, carbohydrate for men, and polyunsaturated fatty acids (PUFA) and selenium for women.

Discussion

In this study, the prevalence of dietary supplement use and its association with demographics, lifestyles, and health characteristics were investigated. The demographics, lifestyle factors, and health characteristics associated with dietary supplement use were sex, age, area of residence, occupation, smoking, BMI, physical activity level, frequency of using prepared foods or eating out, and self-reported stress level. Frequency of alcohol intake was associated only in women. Dietary intake tended to be lower for users of dietary supplements.

A high prevalence of dietary supplement users was observed in metropolitan regions (Suita and Katsushika) and in areas strongly influenced by Western lifestyles (Ishikawa) with ready access to dietary supplements. Associations between supplement use and other demographic factors (sex, age, and occupation) were consistent with results in other studies.[2,4,18–23] In terms of occupation, the lower prevalence in the farming, forestry, and fishing group might reflect their conservative health habits. It might be also a case of one's occupation serving as a surrogate for one's socioeconomic status (SES). A number of studies have indicated a strong association between supplement use and higher income level,[2,4,5,7,20,23] social class,[19] and education.[4,5,20,23,24] Educational background, another factor for SES available only for Cohort I, was also associated with the supplement use.

As for lifestyle and health characteristics, supplement use was associated with healthy lifestyle, which was similar to the earlier-reported tendency for smoking,[4,22,24] BMI, and physical activity.[2,4,7,24,25] Dietary supplement use did not associate with alcohol consumption in men, and was higher in women who drink moderately. Prior studies had reported alcohol consumption in dietary supplement users as either having no association[24] or as showing more users among moderate drinkers.[4,22,26] Supplement users have been characterized as having a positive attitude towards their health. In our study, however, users also showed negative lifestyle factors such as frequent eating out and stressful life. It was assumed that these associations, including moderate drinking among female supplement users, were influenced by urban lifestyle. Such people might be aware of their unhealthy behaviour, and therefore intentionally seek to compensate for it with dietary supplements.

Our results indicated that dietary supplement use could confound the association between dietary intake and disease even after every possible related factor was adjusted. Several earlier studies had found that supplement users consume a more nutrient-dense diet, i.e. low in energy and high in micronutrients.[7,22] In the present study, intakes of both energy and most nutrients were significantly lower for users than non-users of dietary supplements after various factors were adjusted. The results did not change when adjustment was made only for biological factors (age and BMI). The contradiction in the results was assumed to be caused by the complex characteristics of supplement users. Although the SES is usually associated positively with the quality of the diet, some factors such as eating out, which is influenced greatly by SES, can make the association negative.[27] The subgroup analysis in our study indicated that high dietary intake with a higher frequency of eating out made intake of users higher, while low intake with intensive labour such as in farming, forestry, and fishing made intake of users relatively lower.

Table 2 Nutrient intake by supplement users and non-users in the 5-year follow-up survey in Japan Public Health Center Study Cohort II

	Male				Female			
	Users	Non-users			Users	Non-users		
	Mean[c]	Mean[c]	% difference[a]	*P*-value[b]	Mean[c]	Mean[c]	% difference[a]	*P*-value[b]
n	4103	33 195			6776	34 457		
Energy (kcal/day)	1972	2019	−2.4	< 0.01	1774	1829	−3.1	< 0.01
Protein (g/day)	69.8	71.0	−1.8	< 0.01	63.3	64.0	−1.1	< 0.01
Total fat (g/day)	52.0	53.6	−2.9	< 0.01	50.2	51.0	−1.6	< 0.01
Total fatty acid (g/day)	46.4	47.8	−3.0	< 0.01	44.8	45.6	−1.7	< 0.01
SFA[d] (g/day)	15.2	15.9	−4.6	< 0.01	14.7	15.3	−3.9	< 0.05
MUFA[e] (g/day)	19.4	19.9	−2.5	< 0.01	18.7	18.9	−0.9	< 0.05
PUFA[f] (g/day)	11.1	11.4	−2.0	< 0.01	10.8	10.8	−0.5	0.12
n-3 PUFA[f] (g/day)	2.7	2.7	−2.2	< 0.01	2.6	2.6	−0.7	0.12
n-6 PUFA[f] (g/day)	8.4	8.5	−2.0	< 0.01	8.1	8.1	−0.5	0.12
Carbohydrate (g/day)	266.8	266.5	0.1	0.70	228.8	227.5	0.5	< 0.01
Calcium (mg/day)	446	481	−7.8	< 0.01	443	479	−8.3	< 0.01
Phosphorus (mg/day)	1090	1120	−2.7	< 0.01	1000	1028	−2.8	< 0.01
Iron (mg/day)	8.6	8.9	−2.7	< 0.01	8.3	8.4	−1.6	< 0.01
Sodium (mg/day)	3991	4028	−0.9	0.07	3815	3812	0.1	0.83
Potassium (mg/day)	2488	2602	−4.5	< 0.01	2425	2523	−4.0	< 0.01
Retinol (μg/day)	350	362	−3.6	< 0.05	290	309	−6.5	< 0.01
Carotene (μg/day)	1759	1918	−9.0	< 0.01	2023	2148	−6.2	< 0.01
α-carotene (μg/day)	211	235	−11.4	< 0.01	242	261	−7.8	< 0.01
β-carotene (μg/day)	1326	1435	−8.2	< 0.01	1561	1655	−6.0	< 0.01
Lycopene (μg/day)	1173	1417	−20.7	< 0.01	853	1079	−26.5	< 0.01
Vitamin B_1 (mg/day)	1.03	1.05	−2.3	< 0.01	0.95	0.97	−1.8	< 0.01
Vitamin B_2 (mg/day)	1.36	1.44	−5.4	< 0.01	1.32	1.39	−5.5	< 0.01
Niacin (mg/day)	16.7	16.8	−0.8	0.05	15.2	15.2	−0.2	0.60
Vitamin C (mg/day)	101	107	−6.8	< 0.01	107	113	−5.2	< 0.01
Cholesterol (mg/day)	260	268	−3.4	< 0.01	235	239	−1.9	< 0.01
Vitamin B_6 (mg/day)	1.55	1.57	−1.3	< 0.01	1.38	1.40	−1.7	< 0.01
Vitamin B_{12} (μg/day)	8.2	8.4	−2.6	< 0.01	7.4	7.5	−1.5	< 0.05
Folate (μg/day)	251	260	−3.4	< 0.01	243	249	−2.6	< 0.01
Selenium (μg/day)	104	106	−1.6	< 0.01	95	96	−0.7	0.07
Total dietary fibre (g/day)	10.5	11.0	−5.0	< 0.01	10.4	10.9	−4.3	< 0.01
Water-soluble fibre (g/day)	1.5	1.6	−7.8	< 0.01	1.6	1.7	−6.4	< 0.01
Water-insoluble fibre (g/day)	7.0	7.3	−4.2	< 0.01	7.1	7.4	−3.7	< 0.01
Daidzein (mg/day)	8.4	8.9	−5.6	< 0.01	8.0	8.5	−6.4	< 0.01
Genistein (mg/day)	13.8	14.6	−6.0	< 0.01	13.2	14.1	−6.7	< 0.01

[a] % difference was calculated by dividing mean nutrient intake of users minus non-users by mean nutrient intake of users.

[b] *P*-value for difference of geometric mean nutrient intakes between users and non-users.

[c] Geometric mean intake from foods. Energy intake was adjusted for area of residence, age, occupation, smoking, frequency of alcohol consumption, body mass index, physical activity, frequency of miso soup and prepared foods, eating-out, work hours, and stress level. Other nutrients were also adjusted for energy intake in addition to those variables.

[d] Saturated fatty acid.

[e] Monounsaturated fatty acid.

[f] Polyunsaturated fatty acid.

To our knowledge, the present study is the first investigation into the supplement use and its associations with demographics, lifestyles, and health characteristics in a large population in Japan. Only a few smaller studies have so far reported the characteristics of dietary supplement users in Japan.[16,28] The strengths of our study were its population-based large sample, and various and extensive data on potential confounding factors such as demographics, lifestyles, and health characteristics of individuals, as well as dietary supplement use. Those factors can be adjusted later on when the association between supplement use and mortality or disease is investigated. Furthermore, if such association is found, supplement use itself may need to be adjusted when investigating the association between those factors and disease.

One of the limitations of our study was its lack of sensitive SES data, such as income or education level of the participants. Socioeconomic status is strongly associated with supplement use as a result of difference in perception of health and economic status. The positive association with frequency of eating out might be the influence of higher SES level in users, whereas the negative association with prepared food, which tended to be consumed by those who eat at home, might be the influence of low SES.

Generalization of the results could be limited because of the non-respondents to the questionnaire, as well as the representativeness of the study sample. A difference in mortality was observed between the respondents and non-respondents to our baseline questionnaire.[29] For the rural areas where the response rate was 77–90%, the results were probably good estimates for those populations. For the urban areas, however, where the response rate was as low as 40%, supplement use might have been lower in the non-respondents since both the respondents and supplement users tended to have a healthier lifestyle. Furthermore, the overall prevalence might not represent general population in Japan because no statistical weighting

was made for population estimates. However, the characteristics of supplement users were presumably generalizable because the results of subgroup analysis were similar among all areas.

In the present study, we only focused on dichotomous information on dietary supplement use (i.e. user versus non-user) since we aimed to characterize the behaviour of individuals who use dietary supplements. Although we did not examine the amounts consumed or length of dietary supplement use, they may well be of great importance because the association with a disease might depend on them. Further investigation should be done using available data on brand names, frequency and duration of usage in our study. The development of a database for supplement composition is necessary since it is not currently available.

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The JPHC Study Group

The investigators and participating institutions in the JPHC Study Group (Principal investigator: S Tsugane), were as follows: S Tsugane, S Sasaki, Epidemiology and Biostatistics Division, National Cancer Center Research Institute East, Kashiwa; T Sobue, Cancer Information and Epidemiology Division, National Cancer Center Research Institute, Tokyo; J Ogata, S Baba, National Cardiovascular Center, Suita; F Saito, A Koizumi, Y Sano, Iwate Prefectural Ninohe PHC, Ninohe; Y Miyajima, N Suzuki, S Nagasawa, Y Furusugi, Akita Prefectural Yokote PHC, Yokote; H Sanada, Y Hatayama, Kobayashi, H Uchino, Y Shirai, T Kondo, R. Sasaki, Nagano Prefectural Saku PHC, Saku; Y Kishimoto, E Tanaka, M Kinjo, T Fukuyama, Okinawa Prefectural Ishikawa PHC, Ishikawa; K Imoto, H Yazawa, T Seo, A Seiko, F Ito, Katsushika PHC, Tokyo; A Murata, K Minato, K Motegi, T Fujieda, Ibaraki Prefectural Mito PHC, Mito; K Matsui, T Abe, Niigata Prefectural Kashiwazaki PHC, Kashiwazaki; M Doi, Y Ishikawa, A Terao, Kochi Prefectural Chuo-higashi PHC, Tosayamada; H Sueta, H Doi, M Urata, Nagasaki Prefectural Kamigoto PHC, Arikawa; H Sakiyama, N Onga, H Takaesu, Okinawa Prefectural Miyako PHC, Hirara; F Horii, I Asano, H Yamaguchi, K Aoki, S Maruyama, Osaka Prefectural Suita PHC, Suita; S Matsushima, S Natsukawa, Saku General Hospital, Usuda; S Watanabe, M Akabane, Tokyo University of Agriculture, Tokyo; M Konishi, Ehime University, Matusyama; H Iso, Tsukuba University, Tsukuba; H Sugimura, Hamamatsu University, Hamamatsu; Y Tsubono, Tohoku University, Sendai; N Kabuto, National Institute for Environmental Studies, Tsukuba; S Tominaga, Aichi Cancer Center Research Institute, Nagoya; M Iida, S Sato, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; the late M Yamaguchi and Y Matsumura, National Institute of Health and Nutrition, Tokyo.

KEY MESSAGES

- Dietary supplement users had a healthier and more urban lifestyle than non-users in the Japan Public Health Center-based prospective study on cancer and cardiovascular disease (JPHC Study).
- Dietary supplement use was associated with sex, age, area of residence, smoking, body mass index, physical activity level, frequency of eating prepared food and eating-out, self-reported stress level, and dietary intake. Frequency of alcohol consumption was associated only in women.
- The demographics, lifestyles, health characteristics, and dietary intakes might be adjusted when evaluating the effect of dietary supplements on disease since they can become potential confounding factors. The use of supplements may also become a confounding factor when investigating the association between disease and demographics, lifestyles, health characteristics, or dietary intakes.

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Commentary: Vitamin supplement use and confounding by lifestyle

Katherine J Hoggatt

The role of micronutrients in the development of chronic disease remains unclear. A number of observational studies have suggested a protective effect of various nutrients—e.g. folic acid and vitamin E with coronary heart disease, antioxidant vitamins, and cancer. However, recent reviews of the literature have described inconsistencies among studies and conflict between the results of observational research and clinical trials.[1,2] One explanation for these discrepant findings is that results from observational studies of micronutrient intake and disease may be confounded by variables associated with a 'healthy lifestyle'.[3–6] As one review of supplement use and cancer put it, '[s]upplement use may be a behavioral marker for other factors related to cancer risk ... Control in analyses for

Department of Epidemiology, UCLA School of Public Health, Box 951772, Los Angeles, CA 90095–1772, USA. E-mail: khoggatt@ucla.edu