major health-related behaviors may reduce this confounding effect, but completeness of adjustment can never be assured'.[1] The argument for confounding by lifestyle seems plausible—even in studies of total micronutrient intake, those with the highest intakes tend to be supplement users and numerous studies have shown that supplement use is associated with leading a healthier lifestyle. For example, research in Western populations has found that compared with non-users, supplement users tend to be older and leaner, have higher incomes and education, and are more likely to be female and Caucasian; in addition, they are less likely to smoke or drink heavily and generally consume healthier diets and exercise more than non-users do.[7–12]

Several recent studies have described supplement use in new populations and have expanded our understanding of supplement users (e.g. suggesting that supplement users tend to believe in a diet—cancer connection, are more likely to receive cancer-screening tests, take other medications for disease prevention, and have different underlying medical conditions than do non-users[1,9,10,13]). The current article by Ishihara *et al.*[14] is an interesting addition to the literature—it is one of the few conducted in an Asian population,[15,16] and it reports associations for some factors that have not been widely studied, including several that are specific to a Japanese population. Of particular interest are the results suggesting that while supplement use in Japan tends to be associated with aspects of a Western lifestyle, the '... intakes of both energy and most nutrients were ... lower for users than non-users of dietary supplements after various factors were adjusted'. This contrasts with results in Western populations that suggest supplement users consume healthier diets than do non-users.[8,11]

Adjusting for confounding by lifestyle is complicated, even with the information provided by studies such as the current one. For example, several studies suggest that those who take individual-vitamin supplements differ from those who take multivitamins or do not use supplements at all, and there may be differences between those who take one individual supplement versus another.[9,17,18] Many researchers collect detailed data on supplement use as part of a comprehensive nutrition assessment. For example, the authors of the current study asked about '... general use of any vitamin supplements more than once a week, and use of specific supplements by five categories ... For each category, the brand names, frequency, and duration of use were asked.' The authors also tried to ensure correct classification by '[re-categorizing supplements] using brand names according to the definition of dietary supplements in the Women's Healthy Living Eating and Living Study', and they validated this method in another study.[19] Yet in their analyses, the authors considered only a binary 'user versus non-user' outcome, with users defined as anyone '... who used at least one category of dietary supplement one or more times a week for a year or more'. Results for 'supplement users' can obscure important differences, and when a comparison between high and low intake may be a comparison of those who take individual-vitamin supplements versus those who do not,[20] this heterogeneity is important.

A factor related to supplement use (however 'use' is defined) may or may not be a confounder depending on what other variables are controlled in the model. The authors addressed this concern in their dietary-intake analyses (Table 2), stating '... the results [for the full multivariate models] did not change when adjustment was made only for biological factors (age and BMI)'. Their other results (Table 1) are derived from a model in which the variables are mutually adjusted (although the authors do not explain what this means, I assumed the results were from a multivariate model with all variables entered simultaneously). The authors do not say whether these findings would have changed upon using a different subset of the variables in the model. In describing their model selection, they state that they looked at 14 dietary behaviours in relation to supplement use, and '... included in the logistic model the only three variables as dietary habits associated with supplement use'. But they do not say how they decided what constituted an association. Their text hints that this decision was made by significance tests. In particular their Results section describes associations primarily as 'statistically significant' or not (presumably at the 0.05 level, although this is not stated). However, statistical significance says little about the magnitude or precision of an estimated association, and is especially misleading when its absence is misinterpreted as absence of an association. Absence of significance signifies only that the association was estimated too imprecisely to determine the direction with confidence, and often reflects more the limited size of the sample than the size of the association. This and numerous other problems with significance tests have led many methodologists and editors to actively discourage their use in favour of CI and related techniques.[21–29] Table 1 presents CI for many associations, but the Results section suggests that the authors interpreted (and perhaps disregarded) certain associations based more on their 'statistical significance' than their magnitude or precision.

When a model selection strategy uses statistical significance as a criterion for including or excluding variables, it can lead to downwardly biased estimates for the coefficient standard errors (ref. 29, p. 402). In Table 1 we are only shown results from one final model, with little description of how the model was chosen or the sensitivity of the results to its specification; hence, in the present context we cannot know the severity of this bias. Nonetheless, based on methodological studies cited elsewhere (ref. 29, p. 402), I suspect that the results reported by Ishihara *et al.* are much less accurate (and less significant!) than their CI and *P*-values convey.

Finally, the authors give little detail on how their variables were measured, and they do not say whether the cutpoints used for the lifestyle variables reflect the categories used on the questionnaire or if they were chosen by some other criterion. For example, it is not clear how to use their finding that supplement use is associated with stress, when no detail is given on how they determined an individual's stress level or what the categories 'High', 'Medium', and 'Low' represent. For other variables, the cutpoints reflect understandable quantities, but it is still not clear how they were chosen. (The authors do not say if these details are given in other papers based on these data, but they do give references for in-press articles that may have this information.[30,31]) Poor category choices can obscure dose—response relations and leave unnecessary residual confounding (ref. 29, pp. 205–07). At a minimum, it would be helpful to know if their results were sensitive to their choice of categories.

Of course, the issues raised above apply to other studies of supplement use: many have employed a dichotomous supplement-use variable, and their results may have been

sensitive to how variables were measured, categorized, and modelled. The current study is valuable in providing results in a seldom-studied population of supplement users. As the authors point out, '[f]urther investigation should be done using available data on brand names, frequency, and duration of usage in our study'. Given the wealth of data the authors have collected, I will look forward to seeing future results.

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Clinical Trial Note

Phase II Study of Cisplatin and 5-Fluorouracil with Concurrent Radiotherapy in Advanced Squamous Cell Carcinoma of the Esophagus: a Japan Esophageal Oncology Group (JEOG)/ Japan Clinical Oncology Group Trial (JCOG9516)

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Background: In Japan, concurrent chemoradiotherapy is the standard treatment for unresectable esophageal cancer. The optimal combination of chemotherapeutic agents and radiotherapy dose remains controversial. The present study consists of a phase II trial of a cisplatin (CDDP)/5-fluorouracil (5-FU) infusion with concurrent radiotherapy in patients with unresectable, advanced esophageal cancer.
Methods: Between March 13, 1996, and April 28, 1998, 60 patients with advanced squamous cell carcinoma of the thoracic esophagus having either T4 tumor or distant lymph node metastasis (M1 Lym) were enrolled in this study. CDDP 70 mg/m^2 was administered on days 1 and 29, and 5-FU 700 mg/m^2/day was administered on days 1–4 and 29–32. Fractionated radiotherapy was performed on days 1–21 and 29–49; a total dose of 60 Gy was delivered at the rate of 2 Gy per fraction.
Results: The overall response rate of all the 60 registered patients was 68.3% (41/60), and the complete response rate was 15% (9/60). The median survival time was 305.5 days, and the 2-year survival rate was 31.5%. One toxicity-related death occurred. The major form of toxicity exceeding grade 2 was found to be myelosuppression; grade 4 toxicity was observed in five patients.
Conclusion: Based on the overall response rate, the results obtained from the present trial do not appear to be promising. However, it is currently suitable for the treatment of patients with unresectable, advanced esophageal cancer because of certain clinical advantages, a higher CR rate and a lower incidence of fistula formation. A phase II/III trial will be started in order to compare low-dose continual CDDP/5-FU infusion and concurrent radiotherapy with the results obtained in this study.

Key words: esophageal cancer – cisplatin – 5-fluorouracil – chemoradiotherapy – phase II study

INTRODUCTION

In Japan, the standard treatment for advanced esophageal cancer has not been established. Although surgery was performed on patients with locally advanced esophageal cancer, the outcome was not satisfactory due to high invasiveness and morbidity. Several clinical trials have been conducted to evaluate the efficacy and safety of radiotherapy and chemoradiotherapy, which could be more beneficial for the patients. Herskovic et al. (1) compared concurrent chemoradiotherapy (using 5-fluorouracil [5-FU] and cisplatin [CDDP] along with radiation) with radiation therapy alone in patients with locally advanced cancer of the thoracic esophagus (T1–3, N0–1, M0). They reported that the 2-year survival rate was 38% in the group that received chemoradiotherapy, and it was significantly higher than that observed in the group that received radiotherapy alone. As a result of this trial, concurrent chemoradiotherapy using 5-FU and CDDP has become a standard treatment for T1–3 disease. However, data regarding

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treatment of patients with more advanced disease are not available. We had previously conducted a phase II trial consisting of chemotherapy, using a combination of 5-FU and CDDP, followed by radiation therapy (sequential radiotherapy) in patients having T4 disease or distant lymph node metastasis (M1 Lym) and demonstrated that the response rate (RR) was 64.4% (2). Although the RR was found to be high in the group having a far advanced disease, it was felt that the concurrent chemoradiotherapy regimen would be more beneficial as compared with the sequential regimen because the radiosensitizing effect could be therapeutically more beneficial for the patients. Therefore, the present phase II trial (JCOG9516) was performed to evaluate the efficacy and safety of concurrent chemoradiotherapy.

Objective

The objective of this study was to evaluate the efficacy and safety of chemoradiotherapy regimen using CDDP/5-FU along with concurrent radiation therapy in order to determine whether this regimen merited further investigation by a phase III trial. The clinical hypothesis was that the above regimen would achieve a higher tumor response with acceptable levels of toxicity as compared to the former phase II trial that utilized a sequential regimen of CDDP/5-FU infusion and radiation therapy. The primary endpoint of this study was the observation of an overall response to this therapy. The secondary endpoints were concerned with the overall survival and toxicity.

SUBJECTS AND METHODS

Patients

Patients with histological proof of advanced squamous cell carcinoma (SCC) of the thoracic esophagus having T4 tumor or distant lymph node metastasis (M1 Lym) were considered to be eligible. Patients with esophagomediastinal fistula were included in this study, whereas those with esophagotracheal or esophagobronchial fistula and distant organ metastases were excluded. The other eligibility criteria were as follows: (i) age $\leq$75 years, (ii) performance status (PS) of 0–2 based on the classification criteria of the Eastern Cooperative Oncology Group, (iii) adequate renal (serum creatinine $\leq$1.2 mg/dl; BUN $\leq$25 mg/dl; creatinine clearance $\geq$60 ml/min), hepatic (total bilirubin $\leq$1.2 mg/dl; GOT $\leq$2.0 $\times$ normal value; GPT $\leq$2.0 $\times$ normal value), pulmonary (PaO_2 $\geq$70 mmHg) and bone marrow (Hb $\geq$10.0 g/dl; WBC $\geq$4000 /μl; platelets $\geq$100 000/μl) functions. Patients having other active synchronous carcinoma, concurrent uncontrolled medical illness, prior chemotherapy or radiation therapy for any neoplasms and pregnant or lactating women were excluded from the study. All patients provided written informed consent before registration in accordance with the policies of the JCOG. After assessment of the inclusion/exclusion criteria, the patients were centrally registered at the JCOG Data Center (JCOG DC); the orders were transmitted by telephone or fax.

Evaluation

Responses were assessed by barium esophagogram, computed tomography (CT) or magnetic resonance imaging (MRI) and esophageal endoscopy in accordance with the 'Guide Lines for Clinical and Pathologic Studies on Carcinoma of the Esophagus' 8th edition (3), issued by the Japanese Society for Esophageal Disease. A complete response (CR) was defined as a complete disappearance of all evidence of tumor without the appearance of new lesions for at least 4 weeks. A partial response (PR) was defined as a $\geq$50% reduction in the sum of the products of the two perpendicular diameters (SPD) of lesions that could be measured in two directions or a $\geq$30% reduction in the sum of the longest diameters of lesions that could be measured in one direction without the appearance of new lesions for at least 4 weeks. No change (NC) was defined as a <50% reduction and <25% increase in the SPD of lesions that could be measured in two directions or <30% reduction and <25% increase in the sum of the longest diameters of lesions that could be measured in one direction without the appearance of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a $\geq$25% increase in the SPD of lesions that could be measured in two directions or in the sum of the longest diameters of lesions that could be measured in one direction or the appearance of new lesions. All responses (CR + PR) were reviewed and confirmed by X-rays, CT scan and endoscopic findings at regular JCOG meetings.

Statistical Analysis

Simon's two-stage minimax design (4) was used to investigate whether the overall response rate (CR + PR) was sufficient to proceed to phase III trials. The sample size was calculated based on an expected response rate of 80% and an acceptable lowest rate of 65%, with both alpha and beta error of 0.1; a total of 60 cases were required. In this design, when the number of responses exceeds 43 of 60 cases, this leads to the rejection of the hypothesis that true response rate is below 65%. Overall response rate was defined as the proportion of patients with CR or PR divided by the total number of registered patients. The confidence intervals for the response rate were based on the exact binomial distribution. Overall survival time was calculated from the date of registration to death due to any cause. Overall survival was estimated by the Kaplan–Meier method, and confidence intervals were based on Greenwoods' formula (5). The toxicity was graded based on the Japan Clinical Oncology Group Toxicity Criteria (6). All analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC) at the JCOG Data Center. The planned accrual period was 2 years, and the follow-up period was set as 2 years after the completion of the accrual.

Treatment

The treatment schedule is summarized in Fig. 1. CDDP 70 mg/m^2 was administered by slow drip infusion on days 1 and 29, and 5-FU 700 mg/m^2/day was administered by continuous

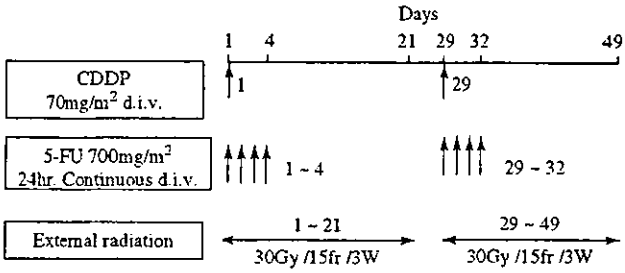

Figure 1. Treatment schedule. CDDP, cisplatin; 5-FU, 5-fluorouracil.

infusion for 24 h on days 1–4 and 29–32. Radiation was administered via a 6~20 MV X-ray. Fractionated radiotherapy was performed on days 1–21 and 29–49, and a total dose of 60 Gy was delivered at the rate of 2 Gy per fraction (one fraction per day and five fractions per week). When the tumor was located in the upper or middle third of the thoracic esophagus, the treatment volume included the bilateral supraclavicular nodes as well as the mediastinum in a T-shaped pattern. When the tumor was located in the lower esophagus, the mediastinum and celiac axis lymph nodes were irradiated. However, in the celiac region, the dose was reduced to 46 Gy to avoid any adverse effect on gastrointestinal function. Oblique fields were used to spare the spinal cord after 40 Gy of radiation was delivered by anterior-posterior opposed pair portals. In the subsequent courses, the dose of CDDP was halved if creatinine level increased to ≥1.3 mg/dl or creatinine clearance decreased to <60 ml/min, and terminated when the creatinine level increased to ≥2.5 mg/dl or creatinine clearance decreased to <40 ml/min. Radiotherapy was suspended when the WBC count decreased to ≤2000/μl or the platelet count decreased to ≤50 000/μl and resumed when the WBC count recovered to ≥3000/μl or the platelet count recovered to ≥75 000/μl within 3 weeks, respectively. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution prior to the initiation of the study. The JCOG Data Center was in charge of the data management.

RESULTS

Between March 13, 1996 and April 28, 1998, a total of 60 patients from 15 institutions were registered in this study. The names of the 15 institutions, the number of registered patients from each institution and the names of the attending physicians are listed in Table 1. Among the 60 registered patients, there were 58 males and two females with a median age of 62 (range 45–74) years; no patients were found to be ineligible. The treatment was terminated in 14 patients for following reasons: disease progression in three patients, toxicities in seven patients, iatrogenic death in one patient, pulmonary tuberculosis in one patient, protocol violation in one patient and refusal of treatment by one patient. The characteristics of the patients and the target lesions are listed in Table 2.

Table 1. Names of the 15 institutions, number of registered patients in each institution and names of the attending physicians

Institution	No. of patients	Attending physicians	
Iwate Medical University	7	K. Ishida	T. Ynagisawa
National Cancer Center East	1	A. Ohtu	T. Ogino
Chiba University	1	K. Isono	T. Ariga
National Cancer Center	8	H. Watanebe	Y. Kagami
Tokyo Women's Medical College	8	H. Ide	T. Okawa
Keio University	8	N. Ando	H. Ito
Tokyo Medical Dental University	2	M. Endo	H. Shibuya
Tokai University	2	T. Mitomi	T. Omosato
Kanagawa Cancer Center	3	H. Koizumi	H. Yamashita
Niigata Cancer Center	7	O. Tanaka	M. Saito
Nigata University	4	T. Nishimaki	K. Sakai
Aichi Cancer Center	5	M. Shinoda	Y. Ito
Kyoto University	1	M. Imamura	Y. Nishimura
Shikoku Cancer Center	2	W. Takiyama	M. Kataoka
Kurume University	1	H. Yamana	M. Jo

Table 2. Patients' characteristics

Characteristic	$n = 60$
Sex	
Male	58
Female	2
Age (years)	
Median	62
Range	45–74
Target lesion (overlapped)	
Esophagus	60
Cervical lymph node	23
Mediastinal lymph node	33
Abdominal lymph node	13
Others	1

Table 3. Response rate and prognosis

No. of eligible patients	60/60 registered patients
Response rate	68.3% (9 CR + 32 PR/60 patients; 95% CI = 55.0–79.7%)
Median survival time	303.5 days (95% CI = 200–387 days)
2-year survival rate	31.5% (95% CI = 19.7–43.3%)

Forty-six (77%) patients completed the treatment regimen. Objective tumor responses observed among the 60 registered patients were as follows: 9 CR, 32 PR, 10 NC and 7 PD. Two patients could not be evaluated. The overall response rate (Table 3) was 68.3% (41/60, 95% confidence interval

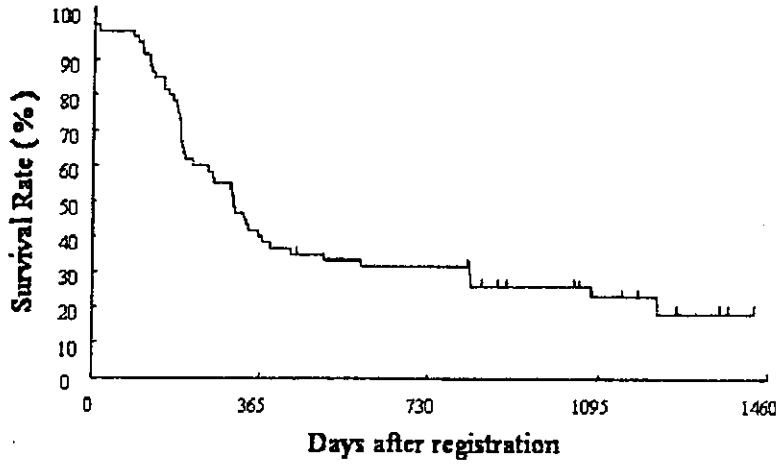

Figure 2. Overall survival among all patients ($n = 60$).

[CI] = 55.0–79.7). Forty-six patients out of a total of 60 died; 43 due to progressive disease, one due to iatrogenic cause and two due to other diseases. At the final follow up in May 2000, 13 patients remained alive, and one patient was lost to follow up. The overall survival curves for all patients are shown in Fig. 2. The median survival time (MST) was 305.5 days (95% CI = 200–387) and the 2-year survival rate was 31.5% (95% CI = 19.7–43.3). The toxicities observed in the patients are summarized in Table 4; hematologic toxicity was observed to be the dominant toxicity. Two iatrogenic deaths (3.3%) were observed either during or immediately following treatment. One patient died of hemorrhage from the tumor on day 6 following the first course, and this was considered to be an iatrogenic death. The other patient died due to sepsis from severe pulmonary infection, 26 days after the end of the treatment. Serious dyspnea was observed in one patient; this might be attributed to the radiation therapy. Grade 4 thrombocytopenia was observed in two patients.

Table 4. Toxicities: no. of cases ($n = 60$)

	Grade					% grade 4
	0	1	2	3	4	
Leukocyte	3	7	30	20	0	0
Neutrophil	14	12	27	5	0	0
Hemoglobin	16	12	28	4	–	0
Platelet	45	7	5	1	2	0
Total bilirubin	48	–	10	1	0	2.5
AST	33	17	7	3	0	0
ALT	32	17	5	6	0	0
PaO_2	23	32	2	0	0	0
Creatinine	52	8	0	0	0	0
Nausea/vomiting	1	27	18	3	–	0
Stomatitis	49	7	4	0	0	0
Diarrhea	50	6	3	1	0	0
Esophagitis	28	22	7	2	0	0
Dyspnea	57	1	0	1	1	1.7
Infection	46	10	3	0	1	1.7
Alopecia	58	2	0	0	0	0
Fever	29	23	8	0	0	0

DISCUSSION

There have been few reports on concurrent chemoradiotherapy for advanced esophageal cancer. Ohtsu et al. (7) reported a 3-year survival rate of 23% in 59 patients having T4 and/or M1 Lym esophageal cancer using definitive CT-RT consisting of 60 Gy irradiation along with CDDP and 5-FU. Furthermore, Nishimura et al. (8) initiated a prospective trial that aimed to evaluate the safety and efficacy of concurrent chemoradiotherapy using a protracted infusion of 5-FU and cisplatin in T4 esophageal cancer patients. They concluded that despite significant toxicity, which could result in the development or worsening of an esophageal fistula, their protocol appeared feasible and effective for the treatment of T4 esophageal cancer patient with or without fistula.

In the present study, the efficacy and safety of concurrent chemoradiotherapy was assessed using 5-FU and CDDP along with 60 Gy of radiotherapy in patients with advanced esophageal cancer in order to develop more effective treatment. The same concurrent chemoradiotherapy regimen used in the US study (1) was used in the present study. The overall tumor RR and CR rate were found to be 68.3 and 15%, respectively. From a statistical point of view, the overall tumor response rate was insufficient to reject the null hypothesis specified earlier in the protocol. One possible reason for this result was excessive expectation regarding the tumor response that could be achieved by this regimen; the expected RR appeared to be much higher than necessary. Although the efficacy of this regimen could not be demonstrated as planned, other efficacy endpoints, such as MST (305 days), 2-year survival rate (31.5%) and grade 4 toxicities (6.7%), were found to be better

than those in the previous study. Ishida et al. (2) investigated the efficacy and safety of sequential chemoradiotherapy in the same patients included in the present study and reported that the overall RR was 64.4%, CR rate was 8.9%, MST was 215 days, 2-year survival rate was 13.3% and life-threatening toxicities (grade 4) were observed in five patients (11%). Therefore, although not based on a direct comparison with sequential chemoradiotherapy, it is concluded that the concurrent regimen is more promising for the treatment of advanced esophageal cancer.

Other trials have used different combinations of chemotherapeutic agents and radiotherapy doses/methods with varying outcomes. John et al. (9) treated 21 patients with 5-FU, CDDP and Mitomycin C (MMC) along with local radiotherapy and reported that the 2-year survival rate was 29% and serious adverse events were observed in five patients (23.8%). Calais et al. (10) initiated a phase II trial that aimed to evaluate the feasibility of a combined treatment using 5-FU, CDDP and MMC chemotherapy and an external radiation dose of 60 Gy in patients with unresectable esophageal cancer and reported that the 3-year survival rate was 27% and WHO grade 4 toxicity rate was 7%. Gaspar et al. (11) conducted a trial of concurrent chemotherapy using 5-FU during both external beam radiation and brachytherapy in patients with potentially curable esophageal cancer and reported that the 1-year survival rate was 49%, MST was 11 months, life-threatening toxicities were observed in 24% patients and iatrogenic deaths occurred in 10% patients. These reports suggest that neither three-drug combination chemotherapy along with radiation nor concurrent chemoradiotherapy along with brachytherapy are more promising than our regimen. It is concluded that the two-drug combination of 5-FU and CDDP along with concurrent radiotherapy is effective and well tolerated. A phase II/III trial is being planned for comparing the regimen used in JCOG9516 and low-dose continuous CDDP/5-FU chemotherapy with radiotherapy (JCOG0303) in order to develop a more effective and less toxic concurrent chemoradiotherapy regimen.

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A Phase II Study of Irinotecan in Combination with 120-h Infusion of 5-Fluorouracil in Patients with Metastatic Colorectal Carcinoma: Japan Clinical Oncology Group Study (JCOG9703)

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Purpose: To evaluate the antitumor effect and feasibility of a combination of irinotecan (CPT-11) and 5-day infusional 5-fluorouracil (5-FU) in a sequential schedule based on our previous combination phase I studies in patients with metastatic colorectal cancer.
Patients and Methods: Forty chemotherapy-naive patients with metastatic colorectal cancer received 90-min infusion of CPT-11 at a dose of 150 mg/m^2 on days 1 and 15 and 120-h protracted infusion of 5-FU at 600 mg/m^2/day on days 3–7, which were repeated every 4 weeks.
Results: The median number of actually administered courses was five, ranging from one to 14. There were 16 (40%) patients who developed grade 3 or 4 neutropenia. Grade 3 or 4 nausea/vomiting and diarrhea were seen in three (8%) and seven (18%) patients, respectively. Only one early death not related to treatment occurred during the study. There was one complete response and 17 partial responses with a response rate of 45% (95% confidence interval: 29.3–61.5%). With a median follow-up period of 22.5 months for survivors, the median survival and median progression-free survival times were 15.9 and 7.0 months, respectively.
Conclusions: Although the toxicities were modest, this sequentially combined regimen is active and feasible in patients with metastatic colorectal cancer.

Key words: irinotecan – 5-fluorouracil – colorectal cancer

INTRODUCTION

Irinotecan (CPT-11) is a camptothecin derivative and is a potent inhibitor of topoisomerase I, a nuclear enzyme involved in the unwinding of DNA (1). CPT-11 was originally developed in Japan and has demonstrated antitumor activity against metastatic colorectal cancer in a single-agent phase II study with a response rate of 27% (2). This activity was confirmed by other studies (3,4). Based on the promising results, we conducted a phase I/II study in combination with 5-fluorouracil (5-FU). At that time, leucovorin had not been commercially available in Japan and we chose a protracted infusion schedule of 5-FU. At first, we used a simultaneous schedule, which consisted of 90-min infusion of CPT-11 immediately followed by 7-day continuous infusion of 5-FU at a fixed dose of 400 mg/m^2/day (5). However, this study demonstrated an unexpected lower response rate of 11% (4/36) and lower incidence of toxicities such as leukocytopenia and diarrhea than those observed in the previous single-agent study. This failure appeared to be caused by a pharmacokinetic interaction between CPT-11 and 5-FU: the plasma area under the concentration × time curve (AUC) of SN-38, an active metabolite of CPT-11, in patients treated with this regimen was 29% lower than the historical control in patients treated with CPT-11 alone. This interaction might be caused by reducing carboxylesterase, a converting enzyme from CPT-11 to SN-38, due to 5-FU (6). We then revised the treatment schedule, applying a 48-h interval between the two agents: CPT-11 was administered on days 1

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and 15 and 5-FU was continuously infused for 120 h from day 3 to day 7 at a fixed dose of 600 mg/m^2/day. This study was carried out as a phase I/II setting with a starting dose of CPT-11 at 100 mg/m^2 and determined a recommended dose of CPT-11 at 150 mg/m^2. In contrast to the previous study, this study demonstrated promising results with a response rate of 32% (8/25) in total and of 42% (8/19) for patients who received a dose of CPT-11 of 125 mg/m^2 or more. This study also showed a promising survival rate with a median response duration of 177 days and no interactions in pharmacokinetic parameters between the two agents as seen in the previous study (7). Based on the results, we conducted a phase II study to estimate the efficacy of this combination regimen. Primary endpoints of this study were response rate and incidence of serious adverse reactions.

PATIENTS AND METHODS

Patient Eligibility

Patients eligible for this study were required to have histologically proven colorectal carcinoma with measurable metastatic lesions. No prior chemotherapy or radiotherapy was allowed. Patients were required to have a 2 or better performance status on the Eastern Cooperative Oncology Group scale with a life expectancy of 8 weeks or longer and to be between 20 and 75 years old. Eligibility also required adequate organ functions as follows: WBC >4000/μl, platelets >100 000/μl, AST and ALT <2.5 times the normal upper limits (except for cases with liver metastasis), serum bilirubin <2.0 mg/dl, blood urea nitrogen <25 mg/dl, creatinine <1.5 mg/dl, creatinine clearance >50 ml/min, normal electrocardiogram and written informed consent from the patients. Exclusion criteria consisted of large amounts of ascites or pleural effusion, brain metastasis, serious complications and any active malignancies at other sites. Pretreatment evaluations included physical examinations, abdominal CT scan, abdominal ultrasonography and chest X-ray. This study protocol was approved by the Japan Clinical Oncology Group (JCOG) Clinical Trial Review Committee and by the institutional review board in each participating institution.

Treatment Schedule

The treatment schedule of this regimen comprised CPT-11 at a dose of 150 mg/m^2 with 90-min infusion on days 1 and 15 and 120-h protracted infusion of 5-FU at 600 mg/m^2/day on days 3–7. This schedule was repeated every 4 weeks until the occurrence of disease progression, unacceptable toxicities or patient's refusal. On every occasion of CPT-11 administration, patients had to fulfil the following criteria: WBC >3000/μl, platelets, >100 000/μl, AST and ALT <2.5 times the normal upper limits (except for cases with liver metastasis), serum bilirubin <2.0 mg/dl, blood urea nitrogen <25 mg/dl, creatinine <1.5 mg/dl, no evidence of diarrhea or infectious fever. Patients had to wait to receive CPT-11 until recovery from any of the above adverse events. If grade 4 hematological toxicity or diarrhea were seen in the previous course or if intervals between any of the two CPT-11 administrations exceeded 21 days owing to any adverse events, then the subsequent dose of CPT-11 was reduced to 120 mg/m^2. Whenever any of the above toxicities occurred despite the dose reduction of CPT-11, the protocol treatment was terminated for the subjects.

Evaluation of Response and Toxicity

The measurable lesions were evaluated by abdominal CT scan and/or chest X-ray, which were carried out in each course. Antitumor activity was evaluated in accordance with standard WHO criteria. Briefly, complete response (CR) was defined as the complete disappearance of all measurable and assessable disease for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or more reduction in the sum of the products of the longest diameter of measurable lesions for a minimum of 4 weeks. No change (NC) was defined as the failure to observe a partial or complete response and progressive disease for at least 4 weeks. Progressive disease (PD) was defined as a 25% or more increase in the sum of the products of the longest diameter of measurable lesions or the appearance of new lesions. Objective responses were confirmed by extramural review.

Physical examinations, blood cell counts, hepatic and renal tests were assessed on a weekly basis in the first course followed by every 2 weeks in the subsequent courses. Toxicity was evaluated according to the toxicity criteria of the JCOG (8), which were based on National Cancer Institute common toxicity criteria.

Statistical Considerations

The sample size for the study was calculated from an expected response rate of 40% and a minimum of 20% with an α and β error of 0.1, using Simon's two-stage minimax design (9). The estimated sample size was 36 and adding 10% of expected ineligible cases, then a total of 40 patients including 19 patients for the first stage were required. Overall survival was calculated from the date of registration to death due to any cause or to the last contact date, using the Kaplan–Meier method. Progression-free survival was analyzed from the date of registration to date of documented disease progression or, if patients died without disease progression, to date of death.

RESULTS

Patients' Characteristics

During the period between October 1997 and May 1999, a total of 40 patients were enrolled and the study was completed without early termination at the first stage. All patients were eligible and their characteristics are listed in Table 1. There were 22 patients with colon and 18 with rectal carcinoma as the primary site. Twenty-six patients had synchronous metastatic diseases at diagnosis and the remaining 14 patients had recurrent metastatic diseases after surgery. Major metastatic sites were liver and lung. Thirty-six patients had received surgical

Table 1. Patients' characteristics

No. of patients	40
Gender, male/female	25/15
Median age (range) (years)	61.5 (37–75)
Performance status, 0/1/2	29/9/2
Colon/rectum	22/18
Histology: well + moderately/poorly differentiated	37/3
Prior surgical resection, yes/no	36/4
Metastatic site:	
Abdominal lymph nodes	18
Liver	22
Lung	20
Others	14

resection for primary tumors before registration. The median number of treatment courses was five, ranging from one to 14. All patients discontinued the treatment and the reasons for leaving the protocol were as follows: 20 patients by disease progression, three by toxicity, nine by patient's refusal related to toxicity of the treatment, seven by refusal not related to toxicity and one by death during the treatment period due to disease progression. There were six patients associated with major deviations: two patients with delay of initiating 5-FU administration on day 3, two with shortened duration of 5-FU administration and two with delay of CPT-11 administration.

Adverse Events

Major adverse events of this combination were hematological and gastrointestinal toxicities. There were five (12.5%), 16 (40.0%) and five (12.5%) patients who developed grade 3 or 4 leukopenia, neutropenia and anemia, respectively. Grade 3 or 4 nausea/vomiting and diarrhea were seen in three (7.5%) and seven (17.5%) patients. Grade 3 liver injury and hyponatremia were observed in one patient each and no other grade 3 or worse toxicities occurred. Discontinuations of the treatment by patient's refusal, described as above, were mostly caused by the gastrointestinal toxicity. However, there was only one early death, within 30 days of the last treatment date. The patient had multiple liver metastases with tumor thrombus on the portal vein at registration and died of hepatic failure 17 days after the last treatment date due to tumor progression. No treatment-related deaths occurred during the study.

Response and Survival

Of the 40 patients, 18 (45%) achieved objective responses including one CR, with a 95% confidence interval (CI) of 29.3–61.5%. The CR case had liver metastasis before registration and showed complete disappearance of metastatic lesion after six courses, which lasted for 1 month. There were 17 (43%) patients with NC and only three (8%) patients showed PD. No significant differences in response rates between metastatic sites were observed: 45.5% (10/22) in liver, 45.0% (9/20) in lung and 50.0% (9/18) in abdominal nodes metastases.

With a median follow-up period of 22.5 months for survivors, the median survival time of the 40 patients was 15.9 months (95% CI: 11.5–19.6 months) with 1-year survival of 62.5% (95% CI: 47.5–77.5%). Median progression-free survival was 7.0 months (95% CI: 5.9–8.3 months) with 1-year progression free survival of 17.5% (95% CI: 5.7–29.3%).

DISCUSSION

CPT-11 has provided survival benefit in patients with metastatic colorectal cancer. First, CPT-11 alone achieved survival prolongation when used as second-line treatment after 5-FU failure as compared with both best supportive care (10) and another scheduled 5-FU treatment (11). These results support the suggestion that CPT-11 can be considered to be the standard treatment after failure of 5-FU-based treatments. Additionally, as first-line therapy, two large randomized studies comparing CPT-11 plus 5-FU–leucovorin with 5-FU–leucovorin in patients with metastatic colorectal cancers have already been reported from Europe (12) and the USA (13). Both studies demonstrated that CPT-11 in addition to 5-FU–leucovorin provided significant prolongation of survival as compared with 5-FU–leucovorin alone: median survival times of the combination arms and 5-FU–leucovorin arms were 17.4 vs 14.1 months in the European study and 14.8 vs 12.6 months in the US study; their median progression-free survivals were 6.7 vs 4.4 and 7.0 vs 4.3 months, respectively. These results suggest that this combination can be a standard treatment for metastatic colorectal cancer.

In our previous combination phase I study of CPT-11 and infusional 5-FU, a simultaneous schedule revealed an antagonism on both toxicity and efficacy (5). We then revised the administration schedule to a sequential format, which was associated with no pharmacokinetic interaction (7). The present phase II study demonstrated efficacy of this combination in terms of median survival and response rate. With respect to the pharmacokinetic and/or pharmacodynamic interaction, Saltz et al. reported that no pharmacokinetic interaction between CPT-11 and 5-FU–leucovorin was observed in their combination phase I study (14). They used a CPT-11 and 5-FU administration schedule in two opposite sequences as 90-min and brief infusions, respectively. The peak plasma concentration and AUC of SN-38 in CPT-11 administration immediately followed by 5-FU and leucovorin were only slightly lower by 13.2 and 8.2%, respectively, than in CPT-11 alone, which showed no significant differences and less clinical importance of the sequence. This combination regimen was then developed into a phase III study showing a survival advantage as compared with 5-FU plus leucovorin. Based on these favorable clinical results, there seems to be no meaningful interactions when 5-FU is used as a bolus infusion. Recently, however, Falcone et al. reported a sequence effect of CPT-11 and 5-FU treatment on the pharmacokinetics and toxicity profile (15). In that study, patients received a 60-min infusion of CPT-11

before or after a 48-h infusion of 5-FU modulated by leucovorin. Their pharmacokinetic analysis revealed that the AUC of SN-38 was 40.1% lower when CPT-11 preceded 5-FU. These results and also our study suggest an interaction of 5-FU with the metabolism of CPT-11 to SN-38 when 5-FU is administered by an infusional schedule, whereas there is no meaningful interaction in a bolus schedule of 5-FU.

The present results demonstrated a high response rate of 45% and favorable survival with a median of 15.9 months. These results clinically confirmed that this sequential schedule with a 48-h interval had at least additive effects and there were no pharmacokinetic interactions. Additionally, the efficacy parameters seemed to be comparable to those of Saltz et al.'s regimen (13) with regard to response rate, 45 vs 39%, and median survival, 15.9 vs 14.8 months. In terms of toxicity, the incidences of grade 3 or 4 diarrhea and neutropenia were slightly lower in the present study than in Saltz et al.'s study; 17.5 vs 22.7% for diarrhea and 40 vs 53.8% for neutropenia. More recently, two large randomized studies revealed that the combined CPT-11 + 5-FU–leucovorin arm developed threefold higher treatment-related deaths than other arms such as 5-FU–leucovorin or oxaliplatin + 5-FU–leucovorin (16). Although the number of the patients in the present study was small, no treatment-related deaths occurred with the present regimen and it appeared to be more manageable than Saltz et al.'s regimen. On comparing the present results with those of Douillard et al.'s regimen (12) using continuous infusion of 5-FU with leucovorin, the efficacy parameters were also similar: response rates 45 vs 41% and median survival times 15.9 vs 17.4 months in our study and in Douillard et al.'s, study, respectively, while grade 3 or 4 diarrhea seemed to be less frequent with our regimen than Douillard et al.'s regimen (17.7 vs 44.4%). These results suggested that our regimen had potentially an efficacy comparable to those of both Saltz et al.'s and Douillard et al.'s regimens without increasing the rate of severe diarrhea. However, in 12 (30%) of the 40 patients in the present study, the treatments were discontinued owing to the toxicity or the patient's refusal related to toxicities. This high incidence of discontinuation related to toxicities appears to be resolved in a future study, partly by using intensive support with anti-emetic or diarrheal agents.

The present study clinically confirmed the efficacy of this combination probably without pharmacokinetic interaction of the two agents. Based on the recent promising results of this combination including leucovorin (12,13), it is now becoming a mainstream treatment for advanced colorectal cancer. However, this study suggested that CPT-11 and a 5-day infusion of 5-FU without leucovorin achieved a favorable response and survival, which were comparable to those with CPT-11 + 5-FU–leucovorin. Additionally, based on our experiences with this combination study series, the timing of administration of each agent should be carefully planned when using an infusional schedule of 5-FU.

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Randomized Trial of Adjuvant Chemotherapy With Mitomycin, Fluorouracil, and Cytosine Arabinoside Followed by Oral Fluorouracil in Serosa-Negative Gastric Cancer: Japan Clinical Oncology Group 9206-1

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Purpose: **To evaluate the survival benefit of adjuvant chemotherapy after curative resection in serosa-negative gastric cancer patients (excluding patients who were T1N0), we conducted a multicenter phase III clinical trial in which 13 cancer centers in Japan participated.**

Patients and Methods: **From January 1993 to December 1994, 252 patients were enrolled into the study and allocated randomly to adjuvant chemotherapy or surgery alone. The chemotherapy comprised intravenous mitomycin 1.33 mg/m^2, fluorouracil (FU) 166.7 mg/m^2, and cytarabine 13.3 mg/m^2 twice weekly for the first 3 weeks after surgery, and oral FU 134 mg/m^2 daily for the next 18 months for a total dose of 67 g/m^2. The primary end point was relapse-free survival. Overall survival and the site of recurrence were secondary end points.**

Results: **Ninety-eight percent of patients underwent gastrectomy with D2 or greater lymph node dissection. There were no treatment-related deaths and few serious adverse events. There was no significant difference in relapse-free and overall survival between the arms (5-year relapse-free survival 88.8% chemotherapy v 83.7% surgery alone; P = .14 and 5-year survival 91.2% chemotherapy v 86.1% surgery alone; P = .13, respectively). Nine patients (7.1%) in the chemotherapy arm and 17 patients (13.8%) in the surgery-alone arm had cancer recurrence.**

Conclusion: **There was no statistically significant relapse-free or overall survival benefit with this adjuvant chemotherapy for patients with macroscopically serosa-negative gastric cancer after curative resection, and there was no statistical difference between the two arms relating to the types of cancer recurrence. We do not recommend adjuvant chemotherapy with this regimen for this population in clinical practice.**

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THE MAIN aim of the adjuvant chemotherapy for curatively resected gastric cancer is to prevent distant recurrence and increase the cure rate of patients. Although gastric cancer with no serosal invasion (S0-1 cancer) has a good prognosis in Japan, about 20% of patients develop recurrence after potentially curative surgery.[1] The most frequent causes for distant recurrence of serosa-negative gastric cancer are hematogenous and lymphatic metastases. Liver recurrence is the most frequent form of failure for serosa-negative gastric cancer.[2] Recently, the results of a phase III clinical randomized trial of mitomycin (MMC) + fluorouracil (FU) + oral tegafur + uracil (UFT) after curative gastrectomy for macroscopically serosa-negative gastric cancer (Japan Clinical Oncology Group [JCOG] 8801) was reported,[3] and it was concluded that patients with T1 cancer could be excluded from future trials because curative surgery alone yielded a high survival proportion, and there seemed to be no need for adjuvant therapy.

No definitive conclusions about the efficacy of adjuvant chemotherapy for gastric cancer have been reached. Encouraged by the favorable results with a regimen of intravenous MMC, FU, and cytarabine (Ara-C) followed by oral FU for stage I and II disease,[4] the Gastric Cancer Surgical Study Group (GCSSG), a subgroup of JCOG, conducted a prospective, randomized, controlled study of adjuvant chemotherapy with MMC, FU, and Ara-C followed by oral FU for serosa-negative gastric cancer after curative gastrectomy. In this study, 13 cancer centers participated. We report the results at median follow-up of 69 months.

PATIENTS AND METHODS

Patients

From January 1993 to December 1994, 252 patients were enrolled in this phase III study. Patients had to fulfill the following eligibility criteria:

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histologically confirmed adenocarcinoma of the stomach; N2 or less lymph node metastasis; macroscopically serosa-negative (S0, no serosal invasion; S1, suspected serosal invasion) cancer resected without residual disease, excluding T1 (cancer invasion to mucosa or submucosa) N0 (no lymph node metastasis); age 75 years or younger; an adequate bone marrow function (leukocyte at least 4,000/mm^3 and platelets at least 100,000/mm^3); adequate liver function (ALT, AST, and total bilirubin no higher than 1.25 times the upper limit of normal range); adequate renal function (blood urea nitrogen and creatinine no higher than 1.25 times the upper limit of normal range); no serious complications equivalent to grade 2 or higher toxicity by JCOG toxicity criteria;[5] no concurrent active malignancy; no history of other malignancy; and provision of written informed consent. Patients were allocated randomly to adjuvant chemotherapy or no further treatment after curative resection. Pathologic specimens were classified as differentiated and undifferentiated carcinoma.

Treatment Assignment and Evaluations

The patients were randomly assigned to the adjuvant chemotherapy or surgery-alone arm by the minimization method of balancing the arms according to the institution and the combination of the macroscopic assessment of tumor extent and lymph node metastasis: S0N0, S0N1, S1N0, S0N2, S1N1, and S1N2. Randomization was performed immediately after surgery through the JCOG Data Center.

The chemotherapy comprised intravenous MMC 1.33 mg/m^2, FU 166.7 mg/m^2, and Ara-C 13.3 mg/m^2 twice weekly for the first 3 weeks after surgery, and oral FU 134 mg/m^2/d for the following 18 months (total maximum dose 67 g/m^2). Usual blood analyses were carried out before each cycle of intravenous treatment. A full blood count was performed every week to assess hematologic toxicity. During the oral administration of FU, each patient was asked to visit the hospital every 2 weeks, and received a physical examination and laboratory check regularly. Patients underwent upper gastrointestinal series, ultrasonography, computed tomography, or other investigations either as required or every 6 months to confirm the evidence of recurrence. Adverse events were recorded according to the JCOG toxicity criteria.[5] Some of the drug adverse effects, such as slight liver damage, may occur even without chemotherapy after surgery; all categories regarded as drug adverse effect were checked also for those patients in the surgery-alone arm for comparison. For the surgery-alone arm, data for these adverse events (except postoperative morbidity and mortality) were collected at the final analysis. The surgery-alone arm received no additional therapy after surgery unless the patient developed a recurrence. The main prognostic factors including age, sex, the extent of serosal and nodal spread, the method and extent of surgery, and histopathologic findings were described according to the general rules issued by the Japanese Research Society for Gastric Cancer Study.[6]

Study Design and Statistical Analyses

This trial was designed as a multicenter, prospective, randomized phase III study. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review boards of participating institutions. The primary end point was relapse-free survival, and overall survival and types of recurrence were also studied as secondary end points. The sample size planned was 220 patients, with 110 patients in each arm. The planned duration of accrual was 2 years and the planned follow-up time was 5 years. This sample size was designed to provide the study with 80% power to detect a difference between 5-year survival of 70% in the surgery-alone arm and 85% in adjuvant chemotherapy arm (hazard ratio, 0.5) with two-sided type I error of 0.05.

Relapse-free survival was measured from the date of random assignment of treatment to the date of the first observation of relapse or the date of death from any cause. If no progression was reported and if the patient had not died, data on relapse-free survival were censored as of the date that the absence of relapse was confirmed. Overall survival was measured from the date of random assignment of treatment to the date of death or the date of the last follow-up. Relapse-free survival and overall survival curves were calculated by the Kaplan-Meier method and compared by the stratified log-rank test with the combination of the macroscopic assessment of tumor extent and lymph node metastasis as strata for all the eligible patients on intention-to-treat basis. The analysis for the toxicity was conducted for all of the randomly assigned patients to evaluate all the toxicity observed in the subjects who received treatments. All the analyses were conducted by SAS software (Version 6.12, SAS Institute, Cary, NC).

RESULTS

Of 252 patients enrolled, one patient in each arm was ineligible. One patient was judged to be ineligible because he was mistakenly enrolled after closure of accrual, and another was ineligible because of age (random assignment of treatment was performed just a few days after the patient's 76th birthday). Therefore, 127 of 128 patients in the chemotherapy arm and 123 of 124 patients in the surgery-alone arm were eligible. All patients in the surgery-alone arm and 80 patients in the chemotherapy arm completed the prescribed treatment. Forty-seven patients in the chemotherapy arm had incomplete chemotherapy because of disease progression in three patients, toxicity in 21 patients, refusal during the treatment in seven patients, protocol violation in four patients, intercurrent death in one patient, and other reasons in 11 patients.

Distribution of the main prognostic factors across the two groups was well balanced (Table 1). Of the 250 patients, 187 (74.8%) were S0, and 245 (98.0%) underwent D2 or more extended lymph node dissection. There were no differences between the two groups in the extent of the cancer, but the proportion of macroscopic type 3 and 4 tumors was slightly higher in the surgery-alone arm than in the chemotherapy arm (P = .002). Twenty-one (8.4%) of the patients had involved serosa on microscopy (T3). There were no lymph node metastases in 139 (55.6%) patients, and 74 patients (29.6%) had a pT1 (pathological mucosal or submucosal cancer) tumor.

Adverse events were generally mild; the frequency of toxic effects of JCOG grade 3 or higher is listed in Table 2. There were three deaths within 30 days after treatment ended in both arms: one patient died of methicillin-resistant *Staphylococcus aureus* colitis 8 days after random assignment of treatment (surgery-alone arm); one patient died of hepatic metastasis 29 days after chemotherapy ended and 193 days after random assignment of treatment (chemotherapy arm); and one patient died of rupture of cerebral aneurysm 10 days after chemotherapy ended and 302 days after random assignment of treatment (chemotherapy arm).

The frequency of postoperative morbidity and mortality was low and is shown in Table 3. There were no significant differences between the groups. Twenty-seven patients (22.0%) in the surgery-alone arm and 32 patients (25.2%) in the chemotherapy arm had at least one postoperative complication (leakage, pancreatic fistula, peritoneal abscess, pneumonia, other infections, stomal stenosis, ileus, second surgery, and hospital death).

At median follow-up of 69 months, 21 patients in the surgery-alone arm and 13 patients in the chemotherapy arm had died. There was no significant difference in relapse-free (Fig 1) and overall survival (Fig 2) between the arms (5-year survival 88.8% [95% confidence interval (CI), 83.2% to 94.3%] in chemotherapy *v* 83.7% [95% CI, 77.1% to 90.2%] in surgery

Table 1. Distribution of the Main Prognostic Factors Across the Two Groups

Prognostic Factor	Surgery-Alone Arm No. of Patients	Surgery-Alone Arm %	Chemotherapy Arm No. of Patients	Chemotherapy Arm %
Sex				
Male	76	61.8	93	73.2
Female	47	38.2	34	26.8
Age, years				
Mean	57.5		58.4	
Range	25-75		33-75	
Serosal invasion				
S0	90	73.2	97	76.4
S1	33	26.8	30	23.6
Dissection of LN				
D1	3	2.4	2	1.6
D2 or more	120	97.6	125	98.4
Macroscopic type				
0, 1, 2, 5	67	54.5	93	73.2
3, 4	56	45.5	34	26.8
Surgical resection				
Total	39	31.7	41	32.3
Distal	81	65.9	84	66.1
Proximal	3	2.4	2	1.6
Curability*				
Absolute curative	112	91.1	123	96.9
Relative curative	11	8.9	4	3.1
Depth of invasion				
m, sm	39	31.7	35	27.6
mp, ss	72	58.5	83	65.4
se	12	9.8	9	7.1
Lymph node metastasis				
N0	64	52.0	75	59.1
N1	42	34.1	38	29.9
N2 or more	17	13.8	14	11.0
JCGC stage				
I	53	43.1	53	41.7
II	61	49.6	67	52.8
III	9	7.3	7	5.5
Histology				
Differentiated	52	42.3	54	42.5
Undifferentiated	71	57.7	73	57.5

Abbreviations: LN, lymph node; JCGC, Japanese Classification of Gastric Cancer; m, mucosal; sm, submucosal; mp, muscularis propria; ss, subserosa; se, serosa exposed. *The absence or presence of residual tumor after treatment. Absolute curative, Ho, Po, ow(-), aw(-), serosal invasion ≤ se, n (+) < R. Relative surative, Ho, Po, ow(-), aw(-) serosal invasion ≤ se, n(+)=R.

*●●●.

Table 2. Adverse Events

Arm of Trial	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3,4
Surgery-alone					
Leukopenia	30	6	0	0	0.0
Hemoglobin	28	41	3	—	2.4
Platelets	4	0	0	1	0.8
Bilirubin	—	41	8	0	6.5
AST	64	23	8	2	8.1
ALT	55	21	17	2	15.3
Creatinine	17	1	2	0	1.6
Nausea or vomiting	7	4	0	0	0.0
Diarrhea	11	2	1	0	0.8
Stomatitis	1	0	0	0	0.0
Chemotherapy					
Leukopenia	39	17	2	0	1.6
Hemoglobin	31	32	2	—	1.6
Platelets	7	1	0	0	0.0
Bilirubin	—	51	16	1	13.4
AST	61	30	10	2	9.4
ALT	58	23	18	1	15.0
Creatinine	14	2	1	0	0.8
Nausea or vomiting	22	4	0	0	0.0
Diarrhea	12	5	0	0	0.0
Stomatitis	3	0	0	0	0.0

alone; $P = .14$, and 91.2% [95% CI, 86.2% to 96.2%] chemotherapy *v* 86.1% [95% CI, 79.9% to 92.2%] surgery alone; $P = .13$, respectively). The results for relapse-free survival were not substantially changed after excluding macroscopic type 4 patients or after adjustment for sex by Cox proportional hazards regression.

Subgroup analyses of the main prognostic factors, such as the extent of serosal and nodal spread, the macroscopic type, pathologic stage, and histologic type in the relapse-free survival and overall survival, also revealed no significant differences between the two arms, but the undifferentiated pathologic type showed better overall survival in the chemotherapy arm than in the surgery-alone arm (5-year survival 95.9% chemotherapy *v* 85.8% surgery alone; $P = .04$; Fig 3).

During follow-up, 17 (13.8%) patients in the surgery-alone arm and nine patients (7.1%) in the chemotherapy arm had a cancer recurrence (Table 4). All of these patients underwent chemotherapy after recurrence. There were no differences between the two arms in the types of recurrence, but hematogenous metastasis (six patients, 4.7%) was the most common type in the chemotherapy arm, whereas peritoneal dissemination (seven patients, 5.7%) was the most common in the surgery-alone arm.

DISCUSSION

No definitive conclusion has yet been drawn from randomized clinical trials of adjuvant chemotherapy for gastric cancer because few studies have shown a positive effect on survival as compared with surgery alone. Meta-analysis is a way of providing the cumulative evidence from several clinical trials. In 1993, Hermans et al[7] published the results of meta-analysis of 11 randomized trials in which postoperative adjuvant chemotherapy

Table 3. Frequency of Postoperative Morbidity and Mortality

	Surgery-Alone Arm (n = 124) No. of Patients	Surgery-Alone Arm (n = 124) %	Chemotherapy Arm (n = 128) No. of Patients	Chemotherapy Arm (n = 128) %
Leakage	4	3.2	4	3.1
Pancreatic fistula	5	4.0	5	3.9
Peritoneal abscess	8	6.5	13	10.2
Pneumonia	1	0.8	1	0.8
Other infections	4	3.2	4	3.1
Stomal stenosis	4	3.2	2	1.6
Ileus	5	4.0	3	2.3
Second surgery	4	3.2	4	3.1
Hospital death	1	0.8	0	0.0

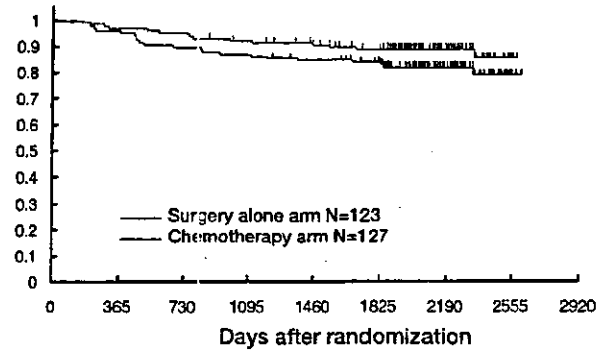

Fig 1. Relapse-free survival. There was no significant difference in relapse-free survival between the arms (5-year survival 88.8% in chemotherapy v 83.7% in surgery alone; $P = .14$).

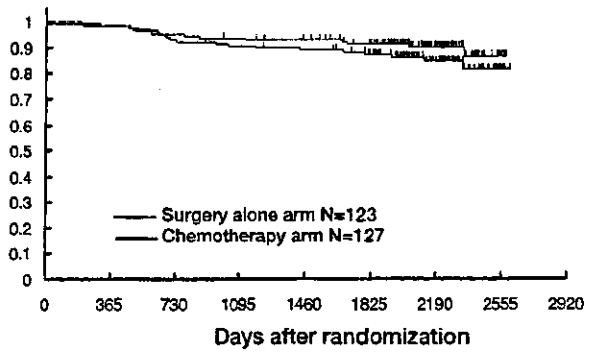

Fig 2. Overall survival. There was no significant difference in overall survival between the arms (5-year survival 91.2% in chemotherapy v 86.1% in surgery alone; $P = .13$).

for gastric cancer was compared with surgery alone. As a result, they found no definitive improvement in the survival (odds ratio, 0.88; 95% CI, 0.78 to 1.08). A recently published update of their analysis indicates a significant survival benefit (odds ratio, 0.82; 95% CI, 0.68 to 0.97).[8] Nakajima et al[9] indicated a significant survival benefit for MMC-based adjuvant chemotherapy after curative resection compared with surgery alone as a result of meta-analysis of six randomized trials (odds ratio, 0.63; 95% CI, 0.51 to 0.79). Recently, Earle[10] evaluated the effect of adjuvant chemotherapy in gastric cancer according to 13 randomized controlled trials in non-Asian countries. They found a significant survival benefit for patients with adjuvant chemotherapy compared with patients with surgery alone (odds ratio, 0.80; 95% CI, 0.66 to 0.97). Subgroup analyses indicated a trend toward a larger effect when analysis was restricted to trials in which at least two thirds of patients had node-positive disease. Mari et al[11] presented results of meta-analysis of 20 randomized trials with a surgery-alone arm. They also demonstrated the survival impact of adjuvant chemotherapy on curative surgery for gastric cancer (hazard ratio, 0.82; 95% CI, 0.75 to 0.89). These meta-analyses indicate that a small but definite survival advantage of adjuvant chemotherapy after curative surgery for gastric cancer, or an even larger advantage for some subgroups of patients, can exist when effective chemotherapeutic regimens with sufficient dose-intensity are used.

The combination therapy of MMC, FU, and Ara-C (MFC)[12,13] produced beneficial effects and favorable results.[14] MFC was reportedly effective for advanced gastric cancer, and it a synergistic effect of the three drugs was observed.[12] Adjuvant MFC combination therapy followed by oral FU therapy had a trend to a better survival in the subgroup of stage I to III patients (17% difference in 5-year survival; $P = .09$)[4] in our former trial, which compared three chemotherapeutic regimens (MFC+FU, MFC+UFT, and MF+UFT). The 5-year survival proportion of each regimen was 70.8%, 62.5%, and 66.7%, respectively. A prospective randomized controlled trial with a surgery-alone arm was therefore planned to prove the efficacy of MFC+FU.

In designing this study, we set a 15% difference in 5-year survival between the arms as clinically significant, which could be modestly and reasonably expected on the basis of the results from previous studies.[4,14] To prove significance in the 15% difference in 5-year survival (85% for the chemotherapy and 70% for the surgery-alone arm) with two-sided type I error of 0.05 and type II error of 0.2, a 2-year accrual time, and 5-year follow-up, a sample size of 110 or more patients per arm was necessary. The number of patients actually enrolled (252 patients) was sufficient for us to detect the planned difference. However, the observed survival difference was smaller than that planned, partly because of much better than expected prognosis of the surgery-alone arm; 5-year relapse-free survival was 88.8% in the chemotherapy arm and 83.7% in the surgery-alone arm, and overall survival was 91.2% in the chemotherapy arm and 86.1% in the surgery-alone arm. With the overall survival of 86.1% in the surgery-alone arm, a 15% improvement in survival because of chemotherapy is clearly impossible. Our study may not have sufficient statistical power for detecting smaller, yet still clinically significant survival benefits from this chemotherapy. Considering its low toxicity, this regimen could be a candidate for future trials to detect smaller clinically meaningful differences for these patients. However, it is also important to find subgroups for which the efficacy of the chemotherapy is expected. In our study, patients with S0 cancer had a good prognosis irrespective of their nodal state or chemotherapy. This finding strongly indicates that most of them had no residual tumor after surgery, and that they were likely to have been cured by surgery alone. These patients accounted for 74.8% of the total, and inclusion of their data may have reduced the overall survival difference between the chemotherapy and surgery-alone arms. This finding indicates retrospectively that our entry criteria were not appropriate in this regard. Subgroup analysis of past trials indicated that adjuvant chemotherapy might show a survival advantage for moderately advanced gastric cancer, such as stages II or III.

Chemotherapy and concurrent radiation therapy (FU + leucovorin + irradiation) suppressed locoregional relapse and showed a significant prolongation of the median survival.[15] This combined-modality therapy was well tolerated and the relapse-free survival was significantly improved. In this trial, however, lymph node dissection was inadequate for enrolled patients with less than D0 for 54% of the patients, D1 for 36% of the patients,

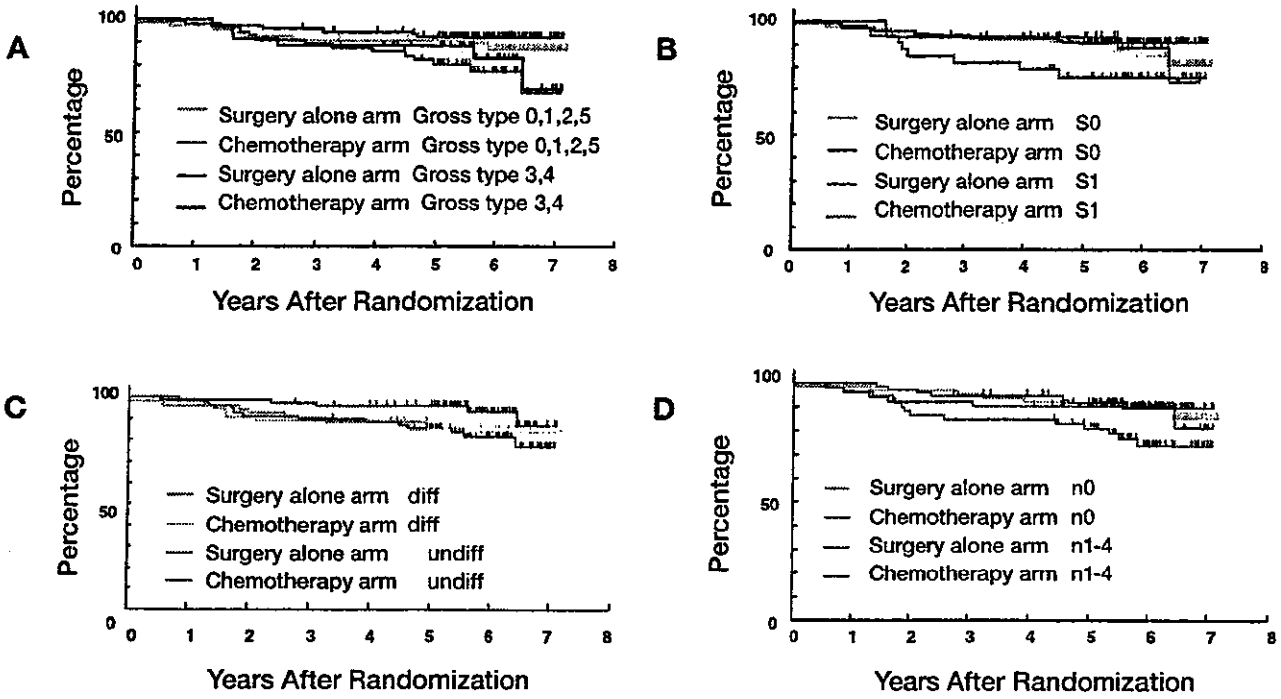

Fig 3. Subgroup analysis: overall survival. Cumulative overall survival of the serosa-negative gastric adenocarcinoma according to macroscopic type (A), serosal invasion (B), histological type (C), and node status (D). Diff, differentiated; undiff, undifferentiated.

and D2 for only 10% of the patients. Considering the high frequency of lymph node metastasis to the first and second nodal stations, contribution of radiotherapy to local control should be enormous. The frequency of D2 or more dissection in our study was 98% and the morbidity and mortality rate was low. For the patients who underwent a curative surgery with D2 or more extended dissection, the necessity of radiation therapy to improve local control is doubtful.

The cost per patient of this adjuvant chemotherapy can be calculated theoretically. The full course chemotherapy costs 604,497 yen ($5,600). The intravenous infusion of MFC costs only 9,966 yen (1.6%) and oral FU for the following 18 months costs 594,531 yen (98.4%).

A clinically significant survival benefit has not been shown in our study, but the results of the study have shown a possible 5% improvement in 5-year survival by the chemotherapy, with the cost per patient of approximately 600,000 yen ($5,600) for the chemotherapy. A low incidence of adverse events and relatively high compliance were observed.

In conclusion, there was no statistically significant relapse-free or overall survival benefit with this adjuvant therapy regimen for patients with macroscopically serosa-negative gastric cancer after curative gastrectomy with D2 or more extended lymph-adenectomy, and there were no major differences between the two arms regarding the types of cancer recurrence. A more than 10% improvement in 5-year survival for this population is unrealistic because of the good prognosis after surgery alone. Studies of adjuvant chemotherapy expecting more than a 10% improvement of 5-year survival for gastric cancer after curative resection should be focused on T3 or a more advanced stage of disease. For serosa-negative patients, large clinical trials to detect smaller but clinically meaningful improvement of survivals with low-toxicity regimens such as MFC+FU are needed.

Table 4. Cancer Recurrence

Site of Recurrence	Arm: Surgery Alone (no. of patients)	Arm: Chemotherapy (no. of patients)	Total (no. of patients)
Peritoneal	7	2	9
Hematologic, liver	4	6	10
Hematologic, other	1	0	1
Local	2	0	2
Distant lymph nodes	2	1	3
Other	1	0	1

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The acknowledgment and appendix are available online at www.jco.org.

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Alcohol Consumption, Smoking, and Subsequent Risk of Colorectal Cancer in Middle-Aged and Elderly Japanese Men and Women: Japan Public Health Center-based Prospective Study

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Abstract

Few studies have examined the association of alcohol consumption and cigarette smoking with colorectal cancer in Asian populations whose genetic susceptibility to these factors are different from Western populations. We investigated this association and the joint effect of these factors, and estimated the population-attributable fraction to clarify the public health impact on a Japanese population, based on a prospective study. We analyzed the 10-year (cohort I) and 7-year (cohort II) follow-up data of the Japan Public Health Center-based prospective study on cancer and cardiovascular disease, derived from 90,004 (42,540 male and 47,464 female) middle-aged and elderly Japanese. We identified 716 (457 in men and 259 in women) newly diagnosed cases of colorectal cancer. Both alcohol consumption and smoking were clearly associated with colorectal cancer in men, after adjusting for age, family history of colorectal cancer, body mass index, and physical exercise. Regular heavy drinking of 150 g/week or more of ethanol showed a statistically significant increased risk compared with nondrinkers: relative risks (RRs) were 1.4 [95% confidence interval (CI), 1.1–1.9] for 150–299 g/week and 2.1 (95% CI, 1.6–2.7) for 300 g/week or more. On the contrary, regular ethanol consumption was not associated with colorectal cancer (RR, 0.7; 95% CI, 0.4–1.1) in women. In terms of smoking, the RRs were 1.4 (95% CI, 1.1–1.8) for current smokers and 1.3 (95% CI, 0.98–1.7) for ex-smokers compared with never-smokers in men. The risk of smoking in women was similar to that in men, although not statistically significant. The colorectal cancer risk with 300 g/week or more of ethanol in current smokers was estimated at 3.0 (95% CI, 1.8–5.1) compared with nondrinkers among nonsmokers in men. Colorectal cancer attributable to alcohol consumption or smoking was estimated to be 46%. In conclusion, approximately half of the colorectal cancer cases may be preventable by tobacco and alcohol controls in middle-aged and elderly Japanese men.

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Introduction

Colorectal cancer is one of the most common cancers in Western countries, and its incidence rate has increased recently in Asian countries, especially in Japan (1), as Japan has been westernized over the past few decades. In fact, the high incidence in Japanese migrants to Hawaii may suggest that a change of environmental factors, including the westernization of dietary habits and lifestyle, may contribute to this increase (1, 2).

Many epidemiological studies have reported the association of alcohol consumption with colorectal cancer (3) and adenoma. Recent prospective studies using incidence data have consistently supported this association (4–11). However, most of such studies of the incidence data have targeted Western populations; an Asian population has been investigated in only

one study (11). Alcohol consumption has increased in Asian populations, especially Japanese, so as to now reach the levels of Western populations (12). At the same time, half of all Japanese people have an atypical allele of the aldehyde dehydrogenase 2 gene (*ALDH2*; Ref. 13), which catalyzes the acetaldehyde metabolism less (14), resulting in a high blood level of acetaldehyde after drinking (15). Because of this genetic polymorphism, Japanese may have a susceptibility to alcohol consumption different from that in Western populations. Therefore, a study using a Japanese population would be expected to detect a stronger effect of alcohol consumption in relation to colorectal cancer than in Western populations.

Studies over the past decade have consistently reported a positive association between smoking and colorectal cancer (16–20). In addition, it has been revealed that smoking requires a long induction period to lead to colorectal carcinogenesis (19, 20). However, evidences of the association and the public health impact of smoking are only available for Western populations (19, 21). It is important to clarify the public health impact of smoking in populations with a high prevalence of smoking like Japanese men (53.5% of males ≥20 years of age in 2000; Ref. 22).

Therefore, we investigated the association of alcohol consumption, smoking, and their joint effect with colorectal cancer and estimated the population-attributable fraction (PAF) to clarify their public health impact, based on a population-based prospective cohort study.

Materials and Methods

Study Population. The Japan Public Health Center-based prospective study on cancer and cardiovascular disease (JPHC study) started in 1990 for the first group (cohort I) and in 1993 for the second group (cohort II). Cohort I covered 5 areas administered by the Public Health Centers (PHC) in 5 prefectures (Iwate, Akita, Nagano, Okinawa, and Tokyo). Cohort II included 6 PHC areas in 6 prefectures (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). Cohort I comprised all residents aged 40–59 as of January 1, 1990 except for Tokyo, and cohort II comprised all residents aged 40–69 as of January 1, 1993 except for Osaka. The study subjects were identified by population registries maintained by local municipalities. When analyzing the present data, we excluded the subjects in Tokyo whose incidence data were not available, and those in Osaka who were not all within the specific age range. Thus, we defined a population-based cohort of 57,714 men (27,063 in cohort I and 30,651 in cohort II) and 59,182 women (27,435 in cohort I and 31,747 in cohort II). Those deemed ineligible during this study period were excluded, such as non-Japanese (29 men and 20 women), those who had already moved away at baseline (94 men and 57 women), and those outside of the 40–59 age parameters in cohort I (2 women). This left 57,591 men and 59,103 women eligible subjects. This study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. The study design is described in detail elsewhere (23).

Baseline Survey. A self-administered questionnaire was distributed mostly by hand and partly by mail to the JPHC study subjects in 1990 for cohort I and in 1993–1994 for cohort II. They were asked about their personal and familial medical histories, smoking, alcohol consumption, dietary habits, and other lifestyle factors (24–26). Among the eligible subjects, 45,452 men (79%) and 49,924 women (84%) returned the questionnaire. From them, we excluded subjects with a self-reported medical history of cancer and with a diagnosis of colorectal cancer before the survey began (687 men and 1,363 women). This additionally reduced the number of eligible subjects to 44,765 men and 48,561 women. Finally, we excluded subjects with incomplete alcohol and/or smoking items (2,225 men and 1,097 women), leaving 42,540 men and 47,464 women as study subjects.

Assessment of Exposure. The average frequency of alcohol consumption was reported in six categories by cohort I: "less than 1 day/month," "1–3 days/month," "1–2 days/week," "3–4 days/week," "5–6 days/week," and "everyday." Subjects consuming alcoholic beverages at least once a week were also asked about types of drinks and average consumption. Subjects in cohort II were asked about drinking status, *i.e.*, never-, ex-, or current drinkers. Ex- and current drinkers provided information on average frequency, types of drinks, and average consumption per day. The average frequency was divided into four categories: "1–3 days/month," "1–2 days/week," "3–4 days/week," and "almost everyday." We assigned a score to each category of frequency as follows: 1.5 for "1–2/week," 3.5 for "3–4/week," 6 for "5–6/week," and "everyday" in the cohort I questionnaire, and 1.5 for "1–2/week," 3.5 for "3–4/week," and 6 for "almost everyday" in the cohort II questionnaire. The amount of ethanol in each type of alcoholic beverages was calculated as follows: 180 ml sake (rice wine) as 23 g ethanol, 180 ml shochu or awamori (white spirits) as 36 g, 633 ml beer as 23 g, 30 ml whiskey or brandy as 10 g, and 60 ml wine as 6 g. Finally, weekly ethanol intake was estimated by multiplying the amount by the score.

Alcohol consumption was classified into five groups in cohort I: nondrinkers (<1 day/month), occasional drinkers (1–3 days/month), and three groups of regular drinkers (1–149 g/week ethanol, 150–299 g/week, and 300 g/week or more; Table 1). Cohort II was categorized into six groups, because nondrinkers were divided into two groups, ex- and never-drinkers. When analyzing the two cohorts together, we combined ex- and never-drinkers into nondrinkers. Three groups of regular drinkers were combined in the analyses of women (Table 2).

To evaluate the validity of alcohol consumption, we compared the estimates from the questionnaires with the 28-day dietary records (7 days in 4 seasons) provided by volunteers in each cohort. Spearman's rank correlations were 0.79 in 94 men and 0.44 in 107 women of cohort I (27), and 0.59 in 176 men and 0.40 in 178 women of cohort II. The reproducibility of the responses on alcohol intake was 0.78 in men and 0.66 in women of cohort I between 1990 and 1995 (5-year interval; Ref. 27), and 0.72 in men and 0.63 in women of cohort II between 1993 and 1997 (4-year interval). Because we also confirmed that assigning a score of 6 to "5–6/week" and "everyday" was as valid as 5.5 to "5–6/week" and 7 to "everyday" in the comparison with the dietary records in cohort I, we used the score 6 in cohort I as well as in cohort II.[3]

The questions on smoking habits included current and former smoking status, age at initiation of smoking, and average number of cigarettes smoked per day. Smoking intensity for current smokers was evaluated by pack-year defined by multiplying the years of smoking times the average number of cigarettes divided by 20 (28). We classified current smokers by the following categories of smoking intensity: <20 pack-years, 20–29 pack-years, 30–39 pack-years, and ≥40 pack-years.

A high prevalence of current smokers was found in both

[3] Unpublished observations.