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ORIGINAL ARTICLE—ALIMENTARY TRACT

Multi-center randomized controlled study to establish the standard third-line regimen for *Helicobacter pylori* eradication in Japan

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Abstract
Backgrounds The present study sought to establish a standard third-line eradication regimen for *Helicobacter pylori* in Japan.
Methods Subjects were 204 patients with *H. pylori* infection in whom the standard Japanese first- and second-line eradication therapies had proven unsuccessful. Patients were randomly assigned to one of the following third-line eradication therapy groups: (1) LA group: lansoprazole (LPZ) 30 mg 4 times a day (qid) + amoxicillin (AMPC) 500 mg qid for two weeks; (2) LAL group: LPZ 30 mg twice a day (bid) + AMPC 750 mg bid + levofloxacin

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(LVFX) 300 mg bid for one week; (3) LAS group: LPZ 30 mg bid + AMPC 750 mg bid + sitafloxacin (STFX) 100 mg bid for one week. Patients for whom these therapies failed underwent a crossover fourth-line eradication regimen. Drug sensitivity was also tested for AMPC, clarithromycin (CAM), MNZ, LVFX, and STFX.

Results Drug resistance rates prior to third-line eradication therapy were 86.4 % for CAM, 71.3 % for MNZ, 57.0 % for LVFX, 8.2 % for AMPC, and 7.7 % for STFX. Intention-to-treat analysis of third-line eradication therapy eradication rates showed a significantly higher rate in the LAS group (70.0 %) compared with the LA group (54.3 %; $p < 0.05$) and the LAL group (43.1 %; $p < 0.001$). The significantly lower rate in the LAL group than the LAS group was caused by bacterial resistance to LVFX.

Conclusions The findings suggest that triple therapy with PPI, AMPC, and STFX for one week would be an effective standard third-line eradication regimen for *H. pylori* in Japan.

Keywords *Helicobacter pylori* eradication therapy · Drug resistance · Levofloxacin · Sitafloxacin · Lansoprazole

Introduction

Helicobacter pylori infection is known to cause various upper gastrointestinal (GI) diseases, from atrophic gastritis and gastroduodenal ulcer to GI mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer [1, 2]. Accordingly, the development of *H. pylori* eradication therapies has been pursued on a global scale. One standard eradication therapy combines a proton pump inhibitor (PPI) with clarithromycin (CAM) and amoxicillin (AMPC), and this triple therapy has been covered under Japan's national health insurance (NHI) scheme since 2000. However, the subsequent increase in bacterial resistance to CAM in Japan caused a decline in the eradication rate of first-line therapy [3], leading to the approval of a second-line eradication therapy substituting metronidazole (MNZ) for CAM in 2007. This second-line therapy has enjoyed a success rate of approximately 90 % [4, 5], but 2–3 % of patients still fail to respond to both first- and second-line therapy. Despite this, however, there is currently no standard eradication therapy in Japan for those failing to respond to second-line therapy, giving rise to expectations for the development of an effective third-line eradication regimen.

While some consider that a third-line eradication therapy should be determined by selecting antibiotics based on tests of the sensitivity of *H. pylori* to each drug [6], clinical drug sensitivity testing is difficult to implement, and previous studies have shown that antibiotics selected on the basis of these results do not always ensure high eradication rates [7, 8].

Consequently, a number of studies have examined the feasibility of a third-line eradication regimen combining a PPI with AMPC (for which *H. pylori* resistance does not tend to develop) for two weeks, or multidrug therapy substituting a new quinolone antibiotic for CAM. AMPC's minimum inhibitory concentration (MIC) for *H. pylori* suggests that the two-week combined regimen of AMPC/PPI would be effective in treating strains that are resistant to CAM and MNZ [3]. In the latter regimen, the most common multidrug combination therapy is a triple regimen

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of PPI, AMPC, and levofloxacin (LVFX), with a reported eradication rate of 60–70 % [9, 10]. Meanwhile, sitafloxacin (STFX) is another new quinolone antibacterial agent with anticipated efficacy due to its low MIC for *H. pylori*, even for LVFX-resistant strains [11]. When combined with PPI and AMPC, STFX is expected to have a good eradication effect, even when used in third-line eradication therapy.

These various study findings suggest that two-week administration of PPI/AMPC and one-week administration of PPI/AMPC/LVFX are both viable options for standard third-line eradication therapy in Japan. However, further studies are required to identify even more effective regimens, and one-week administration of PPI/AMPC/STFX is a strong candidate. Although several types of PPIs are covered under Japan's NHI program for *H. pylori* eradication therapy, lansoprazole (LPZ) was selected in the present study as a potent inhibitor of gastric acid secretion [12]. In Japan, LPZ/AMPC/CAM and LPZ/AMPC/MNZ are covered by the NHI as first-line and second-line eradication therapies, respectively, with the former regimen having a good eradication rate [13, 14].

The aim of the present study was to establish a third-line eradication therapy best suited to use in Japan by comparing the eradication effect and safety of a novel third-line triple therapy substituting STFX for CAM against those of a two-week regimen of LPZ/AMPC and a one-week regimen of LPZ/AMPC/LVFX, both of which are reported to have achieved a degree of success. Moreover, patients failing to respond to third-line eradication therapy underwent a fourth-line eradication therapy based on a crossover regimen, and the efficacy and safety of this therapy was assessed. The correlation between drug resistances and third-line eradication rate was also determined based on the results of drug sensitivity testing and evaluation of drug MICs.

Subjects and methods

Study design

This was a Japanese multicenter, randomized, controlled, comparative study among three groups (Fig. 1). Invitations to join the study were sent to all members of the Japan GAST Study Group (JGSG). Patients were randomly assigned by computer to one of the following third-line eradication therapy groups: (1) LA group: LPZ 30 mg four times a day (qid) + AMPC 500 mg qid for two weeks; (2) LAL group: LPZ 30 mg twice a day (bid) + AMPC 750 mg bid + LVFX 300 mg bid for one week; (3) LAS group: LPZ 30 mg bid + AMPC 750 mg bid + STFX 100 mg bid for one week (Fig. 1).

H. pylori testing was performed at 8 (±4) weeks after completing the third-line eradication therapy, with patients who failed to respond to therapy subsequently undergoing a crossover fourth-line eradication regimen whereby those for whom LAL and LAS failed were treated with LA and those for whom LA failed were given LAS. Patients whose drug compliance fell below 85 % or who experienced a serious adverse drug reaction (ADR) or GI bleeding during the study treatment were not allowed to continue the study. Study protocols were approved by the institutional review board at each institute and complied with provisions of the Declaration of Helsinki.

Study design

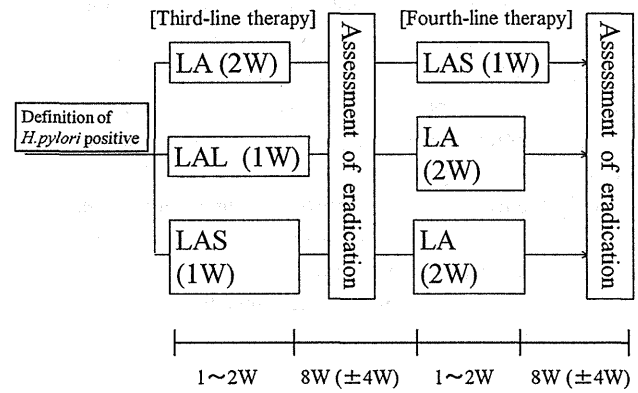

Fig. 1 Study design. Patients were randomly assigned to one of three third-line therapy groups: *LA group* lansoprazole (LPZ) 30 mg qid + amoxicillin (AMPC) 500 mg qid for two weeks, *LAL group* LPZ 30 mg bid + AMPC 750 mg bid + levofloxacin (LVFX) 300 mg bid for one week, *LAS group* LPZ 30 mg bid + AMPC 750 mg bid + sitafloxacin (STFX) 100 mg bid for one week. *H. pylori* testing was performed at 8 (±4 weeks) after completion of third-line eradication therapy, with patients failing to respond to therapy subsequently undergoing a crossover fourth-line eradication regimen whereby those for whom LAL and LAS failed were treated with LA and those for whom LA failed were given LAS

Calculation of the sample size

In the present study, we set the minimum number of registered patients in each group at 50, and the basis for this is given below.

When the study was being designed, there was no published literature on the eradication effects of the third-line eradication regimens investigated herein; there were only conference reports on single-center studies conducted on a small number of subjects. Based on the experience of the research representatives, the eradication rate was estimated to be 50–70 % in the LAL group and 60–80 % in the LA and LAS groups. It was thought that only 2–3 % of patients receiving eradication therapy failed to respond to both first- and second-line eradication therapies, and the number of patients who could be enrolled during the two-year patient registration period was limited. We therefore set the number of patients by assuming the largest possible

difference in eradication rate. Applying the chi-squared test to a 3 × 2 contingency table, a total of 49 patients per group were required to satisfy the conditions of a significance level of 5 % and a statistical power of 80 %. Taking into account dropouts, we set the minimum number of registered patients at 50 per group and 150 in total. We also decided to investigate the outcomes of fourth-line eradication in the event that no significant intergroup differences were seen in the primary endpoints. In addition, differences in eradication rate among the three groups were investigated by applying the chi-squared test to a 3 × 2 contingency table.

Subjects

A total of 204 patients were registered (Fig. 2) from 23 institutes in the period from September 2009 to August 2011. The study targeted *H. pylori*-infected patients in whom first-line (PPI/AMPC/CAM) and second-line (PPI/AMPC/MNZ) eradication therapy had failed, and who gave their written informed consent to participate. The number of times the first- and second-line eradication regimens were administered was not taken into account.

Patients who met any of the following criteria were excluded from the study: (1) age <20 years or ≥81 years; (2) antibiotic treatment(s) after confirmation of the failure of second-line eradication therapy; (3) PPI treatment(s) within one week of study commencement; (4) habitual steroid or non-steroidal anti-inflammatory drug (NSAID) use, with the most recent use occurring within one month of study commencement; (5) previous medical history of serious renal disorder, liver disorder, or drug hypersensitivity; (6) active peptic ulcer(s); (7) history of gastric ulcer surgery; (8) ineligibility for eradication therapy as determined by a physician; (9) history of allergy to drugs used in this study; (10) serious coexisting illness that could interfere with the study.

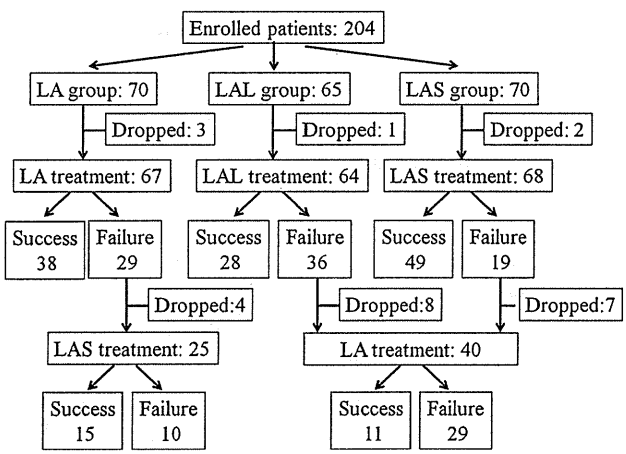

Fig. 2 Assignment of patients and subsequent study flow. The study enrolled 204 patients at 23 sites. Patients were randomly assigned to the LA group ($n = 70$), LAL group ($n = 65$), and LAS group ($n = 70$). Six of the patients taking each third-line treatment did not visit the hospital and dropped out. Third-line therapy was administered to 67, 64, and 68 patients, respectively. Fourth-line therapy was administered to a total of 65 patients for whom third-line therapy failed. Specifically, LAS was administered to 25 patients for whom LA failed, and LA was given to 40 for whom LAL or LAS failed. Nineteen patents taking the fourth-line treatment did not visit the hospital and dropped out

Assessment of *H. pylori* infection and eradication

The presence of *H. pylori* prior to third-line eradication therapy was confirmed with the culture method using tissue samples from the greater curvature of the antrum and the greater curvature from the upper part of the gastric corpus. The culture method was used so that sensitivity testing of the study antibiotics could be done at the same time. When *H. pylori* testing was done using the rapid urease test (RUT), the tissue samples were cryopreserved.

Eradication assessment using the UBT was performed at 8 (±4) weeks after the completion of eradication therapy. The use of PPIs, bismuth preparations, and drugs with antiurease activity such as ecabet sodium was prohibited two weeks prior to third-line eradication testing with the urea breath test (UBT), in order to prevent these agents from affecting the test results.

Drug sensitivity testing

The sensitivity of *H. pylori* to each antibiotic was tested using the agar dilution method. The breakpoint was set at 0.5 μg/mL for AMPC, 1 μg/mL for CAM, 16 μg/mL for MNZ, 1 μg/mL for LVFX, and 1 μg/mL for STFX, and a strain was deemed to be resistant when its MIC value was equal to or exceeded the breakpoint.

Endpoints

The primary endpoint was the third-line eradication therapy eradication rate in the intention to treat (ITT) and per protocol (PP) groups. The secondary endpoints were a comparison of combined third- and fourth-line eradication therapy eradication rates and ADR onset when no intergroup differences were observed in the eradication rates of the respective third-line eradication therapies, and a comparison of the correlations between the sensitivity of *H. pylori* to each antibiotic and the third-line eradication rate.

Statistical analysis

Statistical analysis of intergroup differences in eradication rates was performed using a chi-squared test, and a hazard ratio of ≥5 was deemed significant.

Results

Study subjects and flow

The study enrolled 204 patients at 23 sites around Japan from September 2009 to August 2011. The assignment of patients and subsequent study flow are shown in Fig. 2. Patients were randomly assigned to the LA group ($n = 70$), LAL group ($n = 65$), and LAS group ($n = 70$) (ITT analysis set). Six patients taking each third-line treatment did not visit the hospital and dropped out. Third-line therapy was administered to 67, 64, and 68 patients, respectively (PP analysis set). Fourth-line eradication therapy was administered to a total of 65 patients for whom third-line therapy failed. Specifically, LAS was administered to 25 patients for whom LA failed, and LA was given to 40 for whom LAL or LAS failed. Nineteen patents taking the fourth-line treatment did not visit the hospital and dropped out.

The patient characteristics of the PP analysis set are presented in Table 1. Age (mean ± SD) was 60.3 ± 13.3 years, 55.3 % of patients were men, and reasons for *H. pylori* eradication were *H pylori*-positive gastritis in 73 patients (36.7 %), follow-up of endoscopic stomach cancer treatment in 36 (18.1 %), gastric ulcer in 43 (21.6 %), duodenal ulcer in 31 (15.6 %), and gastric/duodenal ulcer in 6 (3.0 %). Similar patient characteristics were seen in each of the three groups, with no major deviations in age, sex, or reason for eradication therapy.

Third-line therapy eradication rates

Drug compliance for third-line eradication therapy exceeded 90 % in 98.5 % of the LA group, 98.4 % of the LAL group, and 94.1 % of the LAS group, and there were no significant intergroup differences in drug compliance.

ITT analysis of third-line therapy eradication rates (95 % CI) showed that the rate was significantly higher in the LAS group (70.0 %) than in the LA group (54.3 %; $p < 0.05$) and the LAL group (43.1 %; $p < 0.001$) (Fig. 3). In PP analysis (95 % CI), the eradication rate was 56.7 % in the LA group, 43.7 % in the LAL group, and 72.1 % in the LAS group; the rate was significantly higher in the LAS group than in the LAL group ($p < 0.001$) (Fig. 4).

Fourth-line therapy eradication rates

The fourth-line eradication rate (95 % CI) was significantly higher among LAS-treated patients (25 patients from the LA group for whom third-line therapy failed), at 60.0 %, than for LA-treated patients (40 patients from the LAS and

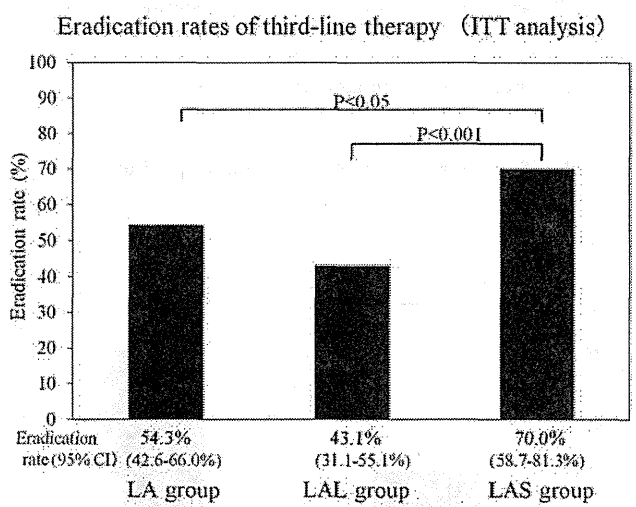

Fig. 3 ITT analysis of third-line therapy eradication rates. The eradication rate was significantly higher in the LAS group (70.0 %) than in the LA group (54.3 %; $p < 0.05$) and the LAL group (43.1 %; $p < 0.001$)

Table 1 Background of patients in this study (PP analysis)

	Total patients	LA ($n = 67$)	LAL ($n = 64$)	LAS ($n = 68$)
Age (mean ± SD)	60.3 ± 13.3	60.3 ± 12.7	61.7 ± 13.1	59.1 ± 14.1
% Male	55.3 %	44.8 %	65.6 %	55.9 %
Disease (*n*)				
Gastritis	73 (36.7 %)	25 (37.3 %)	20 (31.3 %)	28 (41.2 %)
After endoscopic therapy for gastric cancer	36 (18.1 %)	11 (16.4 %)	16 (25.0 %)	9 (13.2 %)
Gastric ulcer	43 (21.6 %)	15 (22.4 %)	13 (20.3 %)	15 (22.1 %)
Duodenal ulcer	31 (15.6 %)	12 (17.9 %)	8 (12.5 %)	11 (16.2 %)
Gastro-duodenal ulcer	6 (3.0 %)	2 (3.0 %)	1 (1.6 %)	3 (4.4 %)
Others	10 (5.0 %)	2 (3.0 %)	6 (9.4 %)	2 (2.9 %)

LA group LPZ 30 mg 4 times a day (qid) + AMPC 500 mg qid for 2 weeks

LAL group LPZ 30 mg twice a day (bid) + AMPC 750 mg bid + LVFX 300 mg bid for 1 week

LAS group LPZ 30 mg bid + AMPC 750 mg bid + STFX 100 mg bid for 1 week

LPZ lansoprazole, *AMPC* amoxicillin, *LVFX* levofloxacin, *STFX* sitafloxacin

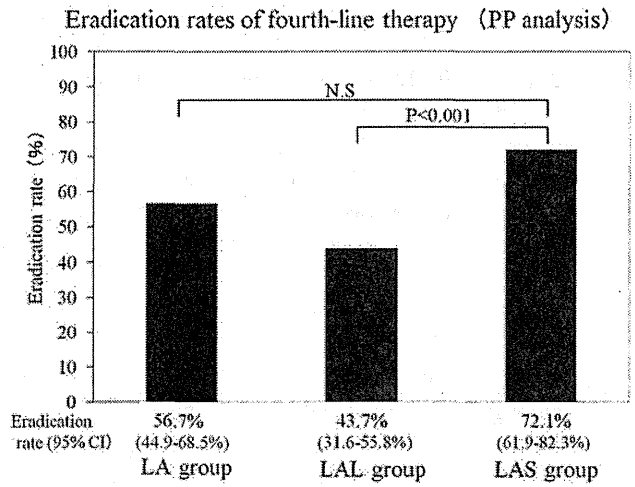

Fig. 4 PP analysis of third-line therapy eradication rates. The eradication rate was 56.7 % in the LA group, 43.7 % in the LAL group, and 72.1 % in the LAS group; the rate was significantly higher in the LAS group than in the LAL group ($p < 0.001$)

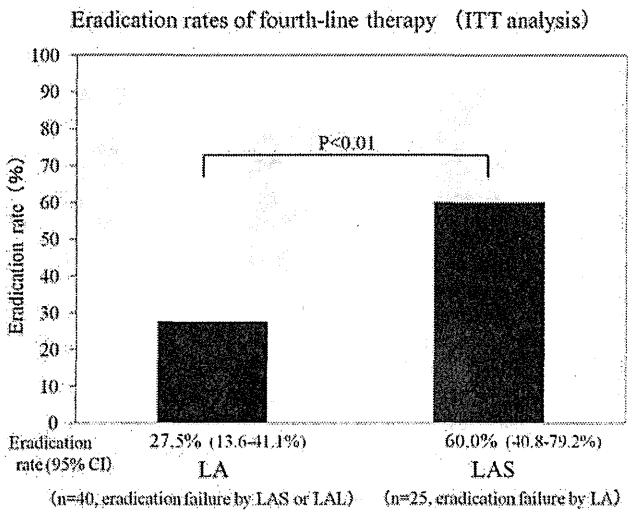

Fig. 5 ITT analysis of fourth-line eradication rates. The eradication rate was significantly higher in the LAS group (25 patients from the LA group for whom third-line therapy failed), at 60.0 %, than in the LA group (40 patients from the LAS and LAL groups for whom third-line therapy failed), at 27.5 % ($p < 0.01$)

LAL groups for whom third-line therapy failed), at 27.5 % ($p < 0.01$) (Fig. 5). There was no significant difference in fourth-line eradication rates with the LA regimen between the LAS group [25.0 % (3/12)] and the LAL group [28.6 % (8/28)]. Drug compliance for fourth-line therapy exceeded 90 % in all patients treated with LA or LAS.

Safety

The adverse event (AE) incidence for third-line eradication therapy was 11.9 % in the LA group, 17.2 % in the LAL group, and 16.2 % in the LAS group. The most frequent AE was diarrhea/soft stool, with incidences of 3.0, 10.9, and 16.2 % in the LA, LAL, and LAS groups, respectively. No AEs warranting discontinuation of the study were observed.

The AE incidence for fourth-line eradication therapy was 3.7 % in LA-treated patients and 4.0 % in LAS-treated patients; all of which were due to diarrhea/soft stool.

Table 2 Rates of resistance to antimicrobials

	AMPC	CAM	MNZ	LVFX	STFX
Cases for sensitivity testing	110	110	108	107	104
Cases of resistant strains	9	95	77	61	8
Rates of resistance (%)	8.2	86.4	71.3	57.0	7.7

Supposed breakpoints: AMPC, 0.5 μg/mL; CAM, 1 μg/mL; MNZ, 16 μg/mL; LVFX, 1 μg/mL; and STFX, 1 μg/mL

AMPC amoxicillin, *CAM* clarithromycin, *MNZ* metronidazole, *LVFX* levofloxacin, *STFX* sitafloxacin

Drug sensitivity testing and resistance

The number of drug sensitivity tests and the number of resistant strains detected (resistance rate) are shown in Table 2. This study targeted patients for whom first- and second-line eradication therapy failed, so many bacterial strains were found to be resistant to each of the study antibiotics. For each antibiotic, the following resistance rates were observed at the supposed breakpoints: AMPC, 8.2 % at 0.5 μg/mL; CAM, 86.4 % at 1 μg/mL; MNZ, 71.3 % at 16 μg/mL; LVFX, 57.0 % at 1 μg/mL; and STFX, 7.7 % at 1 μg/mL. As such, resistance rates were high for all drugs, but CAM-, MNZ-, and LVFX-resistant strains were particularly prevalent.

Drug resistance and third-line therapy eradication rates

A comparison of the correlations between drug resistance and eradication rate in the three third-line eradication regimens is shown in Table 3. Significant differences in the eradication rates for LVFX between sensitive and resistant strains in the LAL group ($p < 0.01$) and the LAS group ($p < 0.05$) can be seen. The eradication rate in the LAL group for LVFX-R was particularly low at 11 %, and that in the LAS group for LVFX-S was especially high at 89 %.

Discussion

The present study compared the efficacy and safety of three types of third-line eradication regimens in *H. pylori*-infected patients in whom first- and second-line therapies had already failed. One-week administration of LPZ/

Table 3 Drug resistance and eradication rates (%)

	LA	LAL	LAS	Total
AMPC				
R	50 % (1/2)	0 % (0/2)	80 % (4/5)	56 % (5/9)
S	50 % (16/32)	44 % (14/32)	70 % (26/37)	55 % (56/101)
CAM				
R	48 % (15/31)	39 % (12/31)	73 % (24/33)	54 % (51/95)
S	67 % (2/3)	67 % (2/3)	67 % (6/9)	67 % (10/15)
MNZ				
R	50 % (14/28)	38 % (9/24)	72 % (18/25)	53 % (41/77)
S	50 % (3/6)	56 % (5/9)	69 % (11/16)	61 % (19/31)
LVFX				
R	45 % (9/20)	11 % (2/18)	57 % (13/23)	39 % (24/61)
S	57 % (8/14)	71 %** (10/14)	89 %* (16/18)	74 %** (34/46)
STFX				
R	0 % (0/3)	0 % (0/3)	50 % (1/2)	13 % (1/8)
S	52 % (14/27)	46 % (14/30)	72 % (28/39)	58 %* (56/96)

AMPC amoxicillin, *CAM* clarithromycin, *MNZ* metronidazole, *LVFX* levofloxacin, *STFX* sitafloxacin, *R* resistant strain, *S* sensitive strain

* $p < 0.05$, ** $p < 0.01$

p values are for comparisons of the eradication rates of sensitive strains with the eradication rates of resistant strains in each regime

AMPC/STFX proved to be significantly more effective at eradicating *H. pylori* than the two-week LPZ/AMPC and one-week LPZ/AMPC/LVFX regimens. The LPZ/AMPC/STFX regimen was also well tolerated, suggesting that it would be highly useful in eradication therapy.

In Japan, both first- and second-line eradication therapy have a failure rate of approximately 3 %, based on supposed eradication rates of 70 and 90 %, respectively. However, in a study by Rokkas et al. [10] of 540 *H. pylori*-positive patients, ITT and PP analysis yielded first-line eradication rates of 70.3 and 76 %, respectively, and second-line eradication rates of 69.1 and 73.5 %, respectively, with 30 patients (5.5 %) receiving third-line eradication therapy. Although that study used different eradication regimens to those employed in Japan, the results suggest that the need for third-line eradication therapy in clinical practice may be greater than we imagined.

Among the third-line eradication regimens evaluated in this study, the two-week LPZ/AMPC regimen had a poor eradication rate: just 54.3 % in ITT analysis and 56.7 % in PP analysis. *H. pylori* does not tend to develop resistance to AMPC, so this antibiotic is more effective at eradicating the bacteria than CAM or MNZ [3]. Nevertheless, the results of sensitivity testing in the present study indicated that *H. pylori* resistance to AMPC was in fact relatively high (8.2 %) and the eradication rate was low, implying that a different antibiotic with more potent antibacterial activity was required to increase the eradication rate.

Furthermore, the eradication rate of the one-week LPZ/AMPC/LVFX regimen was even worse than that of the two-week LPZ/AMPC regimen: 43.1 % in ITT analysis and 43.7 % in PP analysis. LVFX has found widespread use in Japan for the treatment of respiratory and urinary tract infections, leading to concerns that *H. pylori* is becoming less susceptible to the drug. In the present study, the LVFX resistance rate reached 57 % in sensitivity testing, lending weight to these concerns of increased resistance. The *gyr*A mutation has been identified as one of the mechanisms responsible for acquired resistance to LVFX [15]. In overseas clinical studies of third-line eradication regimens based on LVFX, Gisbert et al. [9] reported eradication rates of 60 % in ITT analysis and 66 % in PP analysis, while Rokkas et al. [10] reported a rate of 70 % in both ITT and PP analyses, all of which exceed the eradication rates observed in the present study. The eradication rate of LVFX-resistant strains in the LAL group was also markedly diminished at 11 %. Third-line eradication regimens based on LVFX may be standard overseas, but in Japan, where resistance to LVFX is increasing, a different regimen is required for third-line therapy.

Meanwhile, STFX has a low MIC for *H. pylori* [11] and, when combined with PPI and AMPC, is anticipated to have a good eradication effect, even in third-line eradication therapy. Even in the present study, the eradication rate of the one-week LPZ/AMPC/STFX regimen was significantly higher than those of the other two regimens in ITT analysis at 70.0 %, and was significantly higher than that of the one-week LPZ/AMPC/LVFX regimen in PP analysis at 72.1 %. Moreover, the drug sensitivity test results showed that STFX resistance peaked at 7.7 %, compared to 57 % for LVFX. Eradication rates in the LAS group were also affected by LVFX resistance, but a favorable rate of 89 % was seen in LVFX-susceptible strains.

Although limited to observational studies without an established control group, good eradication results have recently been reported in Japan for STFX-based third-line eradication regimens, with Hirata et al. [16] reporting 75 % in ITT analysis and 80 % in PP analysis, and

Matsuzaki et al. [17] reporting 78.2 and 83.6 %, respectively. These findings imply that third-line therapy using this regimen could achieve an eradication rate of at least 70 %, even in patients with CAM- and MNZ-resistant *H. pylori* infections.

Recent drug sensitivity tests have reported that STFX demonstrated an MIC of $\leq$0.5 mg/mL for 105 strains of *H. pylori*, including 44 strains with the *gyr*A mutation [18], and that it can even exhibit antibacterial activity in LVFX-resistant *gyr*A mutant strains [17–19]. Furthermore, a study by Yamamoto et al. [20] evaluating the sensitivity of 105 strains of *H. pylori* (including CAM-, MNZ-, AMPC-, and LVFX-resistant strains) to ten types of antibiotics found that STFX had the lowest MIC50 and MIC90 values at 0.015 and 0.06 μg/mL, respectively.

Meanwhile, the issue of a viable fourth-line eradication regimen for use in cases of third-line therapy failure remains to be addressed. In the present study, LA therapy for patients for whom third-line LAS and LAL treatment failed produced a peak eradication rate of only 27.5 %. The number of LAS eradication therapy failures may have been small, but further research is still needed to identify an effective regimen.

The findings of the present study suggest that triple therapy with PPI, AMPC, and STFX for one week would be an effective standard third-line eradication regimen for *H. pylori* in Japan. We postulate that a first-line eradication therapy consisting of LPZ/AMPC/CAM for one week, a second-line eradication therapy of LPZ/AMPC/MNZ for one week, and a third-line therapy of LPZ/AMPC/STFX for one week might have a cumulative eradication rate of more than 99 %. However, a much better third-line regimen, with an eradication rate exceeding 90 %, needs to be established in the future.

Conflict of interest Mototsugu Kato received lecture fees from Takeda Pharmaceutical Company. Hideyuki Nomura received lecture fees from Daiichi Sankyo Co. Ltd. and MSD. Takahisa Huruta received research grants from Takeda Pharmaceutical Co., Ltd., AstraZeneca KK, Eisai Co., Ltd., and Daiichi Sankyo Co. Ltd.

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Review Article: Strategy for Drug Discovery at Pharmaceutical Companies

Proposal for the Breakdown of Increased Cancer Healthcare Cost and Its Improvement

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Technological progress in the field of cancer treatment can be expected to accelerate in the future, giving hope to such patients. At the same time, there is concern that cancer care will become more expensive. It is indispensable to minimize the economic burden of patients to deliver technological advances in treatment. It is important for the physician engaged in cancer care to recognize the economic burden of patients and to reduce this burden as much as possible. The Cancer Control Act was enacted in 2007 to promote work on cancer control using all the resources of the nation, and this should surely entail financial support. In order to take advantage of innovations in cancer care, reform of the payment system to lighten the economic burden of the patient would be a pressing necessity.

Key words: economic burden – cancer economics – cost of cancer – molecular targeted drugs – healthcare reform

EXPANDING MEDICAL EXPENSES OF CANCER

The national medical care expenditure in fiscal year 2010 in Japan announced at the end of September 2012 was 37 420 200 million yen, an increase of 3.9% compared with the previous fiscal year. The national income ratio, which was 8.1% in 2000, became 10.7%. The medical expenditure tends to increase sequentially when a slump in economic growth is prolonged. As for the medical care expenditure by age group, it was 55.4% for those 65 years old and older, 45.1% for those 70 years old and older and 33.3% for those 75 years old and older. These were 48.3, 37.4 and 25.1%, respectively, in 2000. Rapid aging of the population was found to be the major factor in the increase in medical care expenditures.

The medical care expenditure per capita was 292 200 yen, a record high. This generally represents an increase in each age group, and it is thought that technological progress is a major factor in the increase. The medical care expenditure for cancer in 2010 was 3 031 200 million yen. In total, 498 800 million yen were spent for colorectal cancer, 381 100 million yen for cancer of the trachea, bronchus and lung, 323 900 million yen for stomach cancer, 252 900 million yen for breast cancer and so on. The ratio of the cancer expenditure to the total medical expenditure was 11.2%. The growth rate of expenditures for cancer was 45.7% from 2000 to 2010, while that of the national medical care expenditure was 24.1% (Fig. 1). The increase in the cancer care expenditure is really remarkable.

In order to tackle with the high price of new technology and new therapeutic drugs, Central Social Insurance Medical Council in Japan has begun to discuss the possibility to introduce technology assessment in the actual public health insurance system. The point at issue is how to reduce health-care cost and to improve the quality at the same time. Some indicators such as cost-effectiveness and quality-adjusted life years is taken up for the discussion.

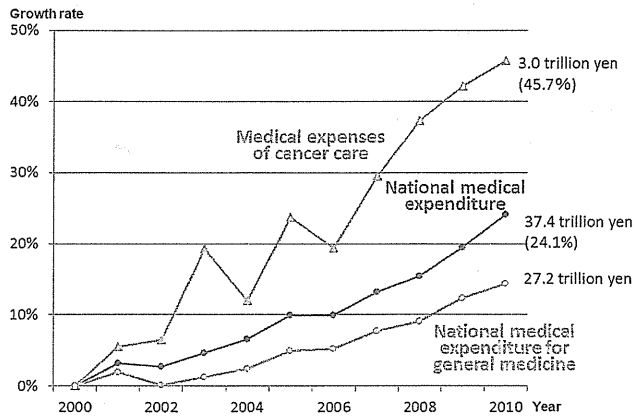

Figure 1. The trend of increase of cancer care expenses from the year 2000. The growth rate of expenditures for cancer was 45.7% from 2000 to 2010, while that of the national medical care expenditure was 24.1

INCREASING ECONOMIC BURDEN OF PATIENTS

Along with the increase in the national medical care expenditure, the economic burden of patients as well as the financial burden of the country became heavier. The co-payment for patients was raised from a fixed charge to 10% in 1984. The ratio of the patient's co-payment was raised from 10% to 20% in 1997 and from 20% to 30% in 2002. Thereafter, the co-payment of 30% (~15% for all ages) has continued. Since the medical care expenditure continued to increase and the co-payment ratio is always 30%, the actual economic burden for the patient increases constantly.

The increase in the cancer care expenditure largely resulted from the increase in the number of cancer patients along with the aging of the population. Simultaneously, rapid technical progress influences the increase in the cancer care expenditure to a great extent. Aging factor and other factors including technical progress have contributed in 46 and 54%, respectively, to the increase in the national medical care expenditure from fiscal year 2007–2008 according to the statistics of Ministry of Health, Labour and Welfare.

The cancer care expenditure per patient increased 9% for 5 years from 2002 through 2007, whereas the average annual salary has decreased 11% from 4.61 million yen in 2000 to 4.12 million yen in 2010 according to National Tax Agency 'Private salary investigation'. This means that the economic burden of patients has become heavier.

The actual situation of the economic burden of patients with cancer is not fully grasped. Therefore, we investigated 40 institutions such as university hospitals and cancer centers through the country (2010 through 2011). This was a self-completed survey asking patients with cancer to list the expenses related to cancer based on a household account book or on the receipts. Moreover, we got clinical information from physicians upon the approval of the patients and conducted a data linkage of the patient survey (1).

As a result, the average annual out-of-pocket expenses for cancer were 864 000 yen ($n = 2022$). The direct expenses of hospitalization, ambulatory care and transportation were 294 000 yen (applicable patients: 68.2%), 259 000 yen and 56 000 yen, respectively. For indirect expenses, the premium of private insurance and cost of alternative medicine were 380 000 yen (applicable patients: 55.0%) and 213 000 yen (32.3%), respectively (Fig. 2).

On the other hand, the refunds and benefits were 624 000 yen on average. The benefits from private insurance, medical refunds and tax refunds were 1 140 000 yen (applicable patients: 43.3%), 242 000 yen (48.2%), 62 000 yen (22.3%), respectively. The substantial economic burden when refunds and benefits were deducted from out-of-pocket expenses was 240 000 yen. Private insurance in Japan complements public insurance, and many patients are aided by this benefit.

For gastric cancer ($n = 158$), the out-of-pocket expenses and the refunds/benefits were 724 000 yen and 664 000 yen, respectively. These were 931 000 yen and 636 000 yen for colorectal cancer ($n = 244$), 1 102 000 yen and 681 000 yen for lung cancer ($n = 302$), 687 000 yen and 496 000 yen for breast cancer ($n = 773$), and 489 000 yen and 246 000 yen for prostate cancer ($n = 102$), respectively. The out-of-pocket expenses and the refunds/benefits differ considerably by types of cancer due to the large variety of treatments and prognosis and so forth.

The out-of-pocket expenses and the refunds/benefits were 1 217 000 yen and 652 000 yen for molecular targeted treatment ($n = 494$), and were 1 156 000 yen and 615 000 yen for the treatment of hematological malignancies, respectively. The out-of-pocket expenses (direct and indirect expenses) were 1 104 000 yen for chemotherapy using Trastuzumab ($n = 206$), 1 160 000 yen for Gefitinib ($n = 61$) 1 242 000 yen for Imatinib ($n = 213$), and 1 533 000 yen for Bevacizumab ($n = 160$), respectively.

DIFFERENCE IN BURDEN BY CLINICAL STAGE

The economic burden differs according to the clinical stage. The out-of-pocket expenses and the refunds/benefits were 610 000 yen and 509 000 yen in Stage I, 683 000 yen and 478 000 yen Stage II, 982 000 yen and 754 000 yen in Stage III, and 1 284 000 yen and 778 000 yen in Stage IV, respectively. The expenditures for alternative medicine and supplements tended to increase with the seriousness of the disease. The annual length of hospital stay was 20.6 days in Stage I, 23.3 days in Stage II, 37.1 days in Stage III and 44.3 days in Stage IV, respectively. The number of visits to hospital was 14.2 times in Stage I, 18.9 times in Stage II, 22.4 times in Stage III, and 24.9 times Stage IV, respectively. Looking at this according to the types of therapy, the length of stay was 27.8 days for surgery, 39.9 days for chemotherapy and 32.6 days for radiotherapy. The number of visits was 18.6 times for surgery, 24.6 times for chemotherapy and 29.3 times for radiotherapy.

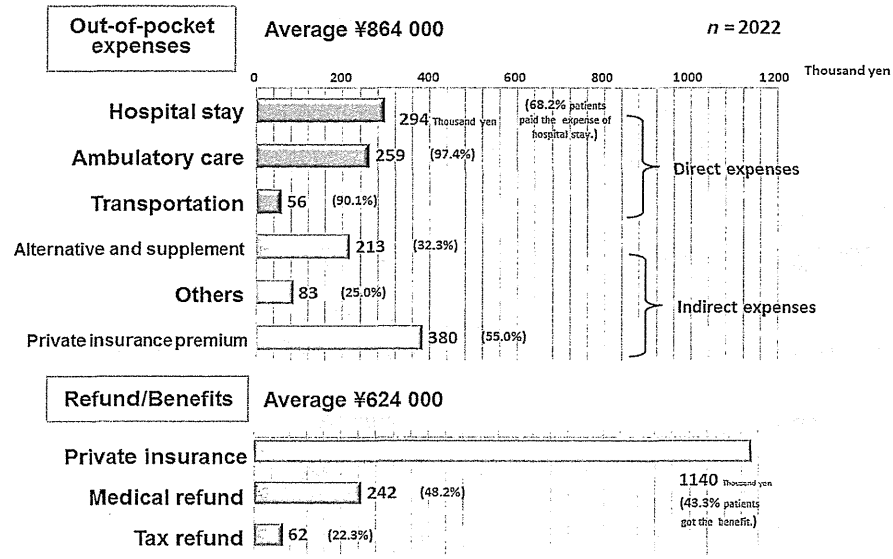

Figure 2. Annual economic burden of cancer patient. The average annual out-of-pocket expenses for cancer were 864 000 yen and the refunds and benefits were 624 000.

The economic burden also differed according to the ratio of the patient's co-payment. The out-of-pocket expenses and the refunds/benefits were 934 000 yen and 746 000 yen with a co-payment of 30% ($n = 1443$ average age 58.5 years old), respectively. In other words, the actual burden was 188 000 yen. However, these were 672 000 yen and 275 000 yen with a co-payment of 10% ($n = 554$, 75.4 years old). In this case, the balance was 397 000 yen, which was heavier than burden with a co-payment of 30%. In case of a co-payment of 10%, the average benefit from private insurance (683 000 yen on average for 32.4% of the patients) and the medical refund (86 000 yen for 54.8% of the patients) are much smaller than that of a co-payment of 30%.

Around 69% of the patients had economic worries ($n = 2037$). The mean out-of-pocket expense (752 000 yen) of the patients without economic worries was three-fourths that of the patients (987 000 yen) with economic worries (Fig. 3). In the viewpoint of promoting work, if the length of stay is shortened and the number of hospital visits is decreased, the patients with cancer would have more working opportunities. For example, in patients with breast cancer ($n = 774$), the average length of stay was 14.1 days and the number of visits was 20.4 times. If the hospitalization included Saturday and Sunday for 4 days and ended on a half day, the suspension of work due to treatments would be almost equal to annual paid holidays.

DECLINING THE TREATMENT DUE TO ECONOMIC REASONS

According to our survey, three-fourths of the patients with colorectal cancer felt that the medical expenses under public insurance were heavy ($n = 232$). Half of the above patients felt that the premium of private insurance and the costs of alternative medicine were also heavy. Many patients think that the indirect expenses are crucial. Sixty percent of patients with colorectal cancer were obliged to withdraw deposits and savings, and 10% managed to pay the medical costs by borrowing from a family member or relative ($n = 249$). In our survey, the average age of patients with colorectal cancer was 64.4 years and a pension was the sole regular income for many patients. For one-third of the above patients, the household income was between 1 million and 3 million yen. For 40% of the above patients, the household savings were less than 7 million yen.

Although medical treatment cannot be denied for economic reasons under Japanese universal health insurance system, patients who refused an expensive therapy have recently increased. According to our survey for physicians engaged in cancer care ($n = 1176$, clinical experience: 17.8 years), 1.6 inpatients and 1.5 outpatients per month gave up the most appropriate treatment due to some economic reason.

Sixteen percent of the above patients had to cancel the scheduled treatment, 56% could not avoid changing the treatment and 13% were obliged to interrupt the treatment. It is an extremely serious situation for patients, and also for their physicians, when patients must forego necessary treatments, especially considering that refunds are available expensive medical treatments. Since molecular-targeted drugs are expensive in general, it is not rare to modify or withdraw these drugs such as Bevacizumab or Sorafenib for the treatment of solid tumors and Rituximab or Imatinib for hematological malignancies. In the case of Bevacizumab, for instance, a planned regimen such as Bevacizmab + XELOX was modified to XELOX. In the same manner, some regimens were modified from Bevacizmab + mFOLFOX6 to mFOLFOX6, and from Bevacizmab + FOLFIRI to FOLFIRI.

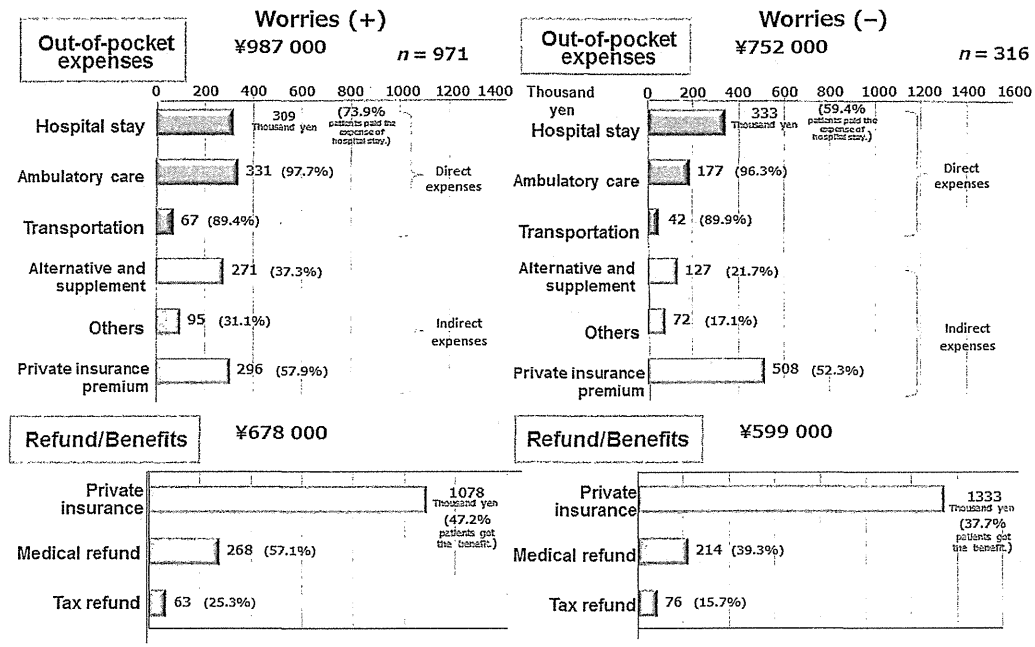

Figure 3. Annual economic burden of cancer patient by worries about economic problems. The mean out-of-pocket expense of patients without economic worries was three-fourths that of the patients with economic worries.

We calculated the change in drug costs on the basis of the payment system for medical services in 2011 (the standard treatment for a male patient of 60 kg and 165 cm) in the above three cases. Drug costs were decreased by 48.6%, from 468 000 yen to 228 000 yen, by 49.8%, from 299 000 yen to 149 000 yen, and by 35.4%, from 232 000 yen to 82 000 yen, respectively. Given the payment system, if one half of the current drug costs is supported by a second or third party, more patients would be able to undergo optimal treatment.

IMPORTANT ROLE OF MEDICAL REFUND SYSTEM

There are limits to the expenses patients must pay based on their income. The medical refund system is a safety net that complements the health insurance system (co-payment of 10–30% by the patient). The government expenditure for medical refunds has doubled during the 8 years from 2000 through 2008 (1713 billion yen), suggesting that the economic burden on patients has been increasing. The medical refund system was founded in 1973, and many regulations were introduced afterwards. User cannot easily understand this complicated system. However, the detailed rules of the system have come to be understood by patients, since this system is requested by the patients the number of users has increased. This system is explained in detail when required in the consultation support center of cancer center hospitals. Forty-eight percent of patients with cancer and 80% of patients administered molecular-targeted treatment applied for this system, which has recently become indispensable. We examined how the medical refund system reduces patients' payments using the survey data. We found that this system lightens the patients' burden by 32.5% on average ($n = 686$) (Fig. 4). These are 35.4% in patients with colorectal cancer and 36.6% in patients from 40 to 49 years old.

MEASURES AGAINST RISING COST OF CANCER TREATMENT

There are many requests for relief from the economic burden from patients with cancer, who want the cost of anticancer drugs to be reduced, the ceiling for reimbursement to be lowered, the percentage of co-payment to be lower than for other diseases and that more information about the economic burden should be given to patients and so on ($n = 236$). Measures corresponding to the patients' suffering from the economic burden of treatment are very urgent. The problem of so-called 'economic refugees with cancer' (patients who cannot undergo the adequate treatment for economic reasons) might be addressed along with the accelerating technological progress.

These measures could be broken down into three levels: physicians' consideration in the clinical setting, better operation of the actual system and drastic healthcare reform. The first level includes the promotion of ambulatory care as an alternative to hospitalization, shortening the duration of hospitalization, reducing excessive testing and medication, the use of cheaper generic drugs and adequate explanation about the costs. The second level includes reductions in the ceiling

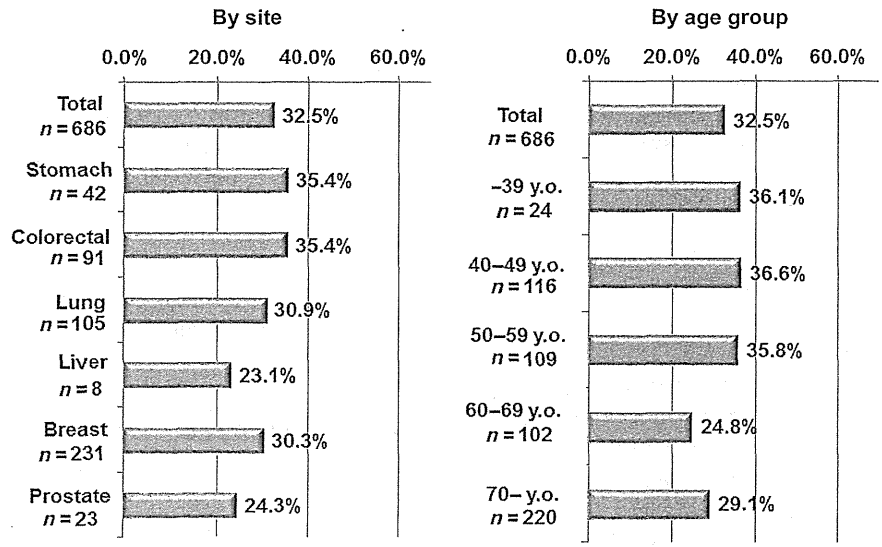

Figure 4. Percent reduce of the patients' payments with medical refund system. The medical refund system lightens the patients' burden by 32.5% on average. y.o., years old.

for reimbursement and improvement of the so-called 'drug lag' (shortening the approval process for new drugs) and 'device lag' (that of new technology). A few patients are obliged to the new drugs by way of the personal import on their own expense.

For the third level, it is necessary to review the proper percentage of co-payments depending not only on age but also on the seriousness or other characteristics of the disease to relieve the excessive economic burden of the patients. The national income has been decreasing while medical costs per person have been increasing for the past decade and there is surely a limit to the economic relief that can be provided by the medical refund system. This is because the payment of medical refunds has greatly expanded and the government will suffer from insufficient funds.

Information about patients' out-of-pocket expenses in other countries would be useful for our healthcare reform, although health insurance systems differ country by country and a simple comparison might lead to misunderstandings. Medical care is free of charge as a rule in such countries as the UK, Canada and Australia (excluding drug costs). The out-of-pocket expenses of a patient is 10 euros per day for hospitalization and 10 euros per quarter for ambulatory care (it is free of charge if there is a letter of introduction) in Germany. There is an upper limit of 80 krona per day (~9600 yen) for hospitalization and an upper limit of 900 krona per year for ambulatory care in Sweden. The economic burden of a patient is rather light in these countries.

The percentage of out-of-pocket payments is 20% for hospitalization and 30% for ambulatory care in France, whose system resembles that of Japan. However, some private insurance can bridge most of the payment gaps, and medical care for 30 diseases including cancer is free of charge. This is an important example of how the heavy economic burden of long-term and expensive treatments can be avoided by patients. That is, it turns out that the out-of-pocket payments in Japan act at a particularly high level for developed countries. It is extremely important to secure necessary healthcare resources from and to drastically rationalize the distribution of medical expenditures. Such reform of the current insurance system is inevitable because of the need to cope with constantly advancing innovation. Healthcare systems in some western countries have introduced the concept of priority (so-called 'triage' not only in emergency medicine but also in general medicine), which serve as a reference *for* Japan.

The total sum of out-of-pocket payments by patients with cancer in Japan comes to 461 billion yen per year based on the data of our survey. Therefore, making cancer treatment free of charge would be possible in Japan if an additional 500 billion yen in public spending were made available. There is little risk of moral hazard (increase of the number of patients and medical expenditures caused by the lack of fee) since the diagnosis of cancer is concrete. Financial support depending on the type of disease is more rational than that depending on the age group (such as charge-free medical care for the elderly ~40 years ago), because the elderly vary in health status significantly even at the same age.

The average age of patients with cancer exceeds 60 years old. The income is restricted to a pension in many cases and the out-of-pocket expenses for cancer treatment are often covered by drawing on savings. When looking at the annual household income (tax included), 31% of the patients earned 1~3 million yen or less and more than half is <5 million yen ($n = 2928$, average age 61.7 years old). As for the amount of household savings, in 40% it was <7 million yen and in half it was <10 million yen. Many senior citizens tend to reduce daily living expenses on the preparation for the high probability suffering from serious illness in the future. The domestic demand is reduced if those of middle

and advanced age, which occupy the majority of the population, refrain from consumption because of worries about future illness. It is essential to stabilize the pension system, but the solution to this problem will likely take time before anxiety about the future is alleviated. Relief from the economic burden of cancer care must be a reasonable certainly for the elderly, and it would be one of the most cost-effective measures to implement.

CONCLUSION

Technological progress in the field of cancer treatment can be expected to accelerate in the future giving hope to such patients. At the same time, there is concern that cancer care will become more expensive. It is indispensable to minimize the economic burden of patients to deliver technological advances in treatment. The economic burden of the patient might influence the outcome of treatment, and the costs would therefore be an important element in high-quality cancer care, as ASCO (American Society of Clinical Oncology) noted (2). It is important for the physician engaged in cancer care to recognize the economic burden of patients and to reduce this burden as much as possible. The Cancer Control Act was enacted in 2007 to promote work on cancer control using all the resources of the nation, and this should surely entail financial support. In order to take advantage of innovations in cancer care, reform of the payment system to lighten the economic burden of the patient would be a pressing necessity.

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Conflict of interest statement

None declared.

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Study Profile

Cohort Profile of the Japan Collaborative Cohort Study at Final Follow-up

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ABSTRACT

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) was established in the late 1980s to evaluate the risk impact of lifestyle factors and levels of serum components on human health. During the 20-year follow-up period, the results of the study have been published in almost 200 original articles in peer-reviewed English-language journals. However, continued follow-up of the study subjects became difficult because of the retirements of principal researchers, city mergers throughout Japan in the year 2000, and reduced funding. Thus, we decided to terminate the JACC Study follow-up at the end of 2009. As a final point of interest, we reviewed the population registry information of survivors. A total of 207 (0.19%) subjects were ineligible, leaving 110 585 eligible participants (46 395 men and 64 190 women). Moreover, errors in coding date of birth and sex were found in 356 (0.32%) and 59 (0.05%) cases, respectively, during routine follow-up and final review. Although such errors were unexpected, their impact is believed to be negligible because of the small numbers relative to the large total study population. Here, we describe the final cohort profile at the end of the JACC Study along with selected characteristics of the participants and their status at the final follow-up. Although follow-up of the JACC Study participants is finished, we will continue to analyze and publish study results.

Key words: JACC Study; cohort study; Japan; follow-up

INTRODUCTION

To evaluate the risk impact of lifestyle factors and levels of serum components on human health, in the late 1980s we established a large-scale cohort study, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study). During a follow-up period of approximately 20 years, data on deaths from major causes such as stomach cancer, lung cancer, and cardiovascular diseases enabled examination of risk factors. We subsequently published results regarding associations between lifestyle factors and health status in almost 200 original research articles in peer-reviewed English-language journals. Additionally, we are currently developing a website to increase public awareness.[1]

The enthusiasm of researchers is always important in promoting a cohort study, but enthusiasm is not enough since such work takes many years to bear fruit. A substantial budget is also required. The JACC Study was started after receiving a promise of funds for 10 years; however, after the initial 10 years had passed, it became necessary to apply for small public grants to maintain and follow cohort participants. In addition, administrative mergers of cities, towns, and villages throughout Japan in the year 2000 sometimes caused further difficulties in following subjects in the study area, due to changes in partnerships between local governmental offices and researchers. Moreover, with the retirement of key researchers, it was not always easy to transfer their work to their successors. As a result of these challenges, we decided to

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terminate follow-up of participants in the JACC Study at the end of 2009.

As a final point of interest, we used population registers in the study area to review the list of survivors. Some subjects were found to be no longer living in the study area, although the overall number of such participants was small. Moreover, a small number of errors in the coding of date of birth and sex were identified during follow-up data collection. Here we describe the final cohort profile obtained upon completion of the JACC Study. Data on cancer incidence have not yet been compiled because of the time lag of the cancer registry system. This process is expected to continue until 2013, at which point incidence information until 2009 will be made available.

METHODS

Study subjects

Details of the study design and concept have been described elsewhere.[2–4] Briefly, the JACC Study was a multicenter collaborative study in which 24 institutions voluntarily participated. Recruitment of study subjects living in 45 areas was managed by individual investigators whose responsibility was to construct the cohort in that area. Data were collected from 1988 through 1990. However, although most baseline surveys were performed during this 3-year period, some subjects were recruited before and after this period because of the need for a preliminary study in 3 areas and later collaboration in 1 area. Individual informed consent before participation in the study was obtained in 36 of the 45 study areas (written consent in 35 areas and oral consent in 1 area); in the remaining 9 areas, group consent from the area leader was obtained. Participant eligibility was verified by individual investigators, who confirmed that (1) the participant was living within the study area and (2) was aged 40 to 79 years at baseline. In addition, date of birth and sex were further verified using official documents and/or a completed self-administered questionnaire.

Follow-up

As follow-up information, dates and causes of death were annually or biannually confirmed, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications) and/or the Ministry of Health, Labor and Welfare, Japan. The date of move-out of cohort members from the study area was also annually or biannually verified by the investigator in cooperation with key members of the local governmental office. In 24 of the 45 areas, data on cancer incidence such as date of diagnosis and primary site were also collected through population-based cancer registers or by reviewing the records of local major hospitals. In most areas, follow-up was completed at the end of 2009; however, it was stopped at the end of 1999 in 4 areas, at the end of 2003 in another 4 areas, and at the end of 2008 in 2 areas.

Final data setup: correction of birth date and sex information, identification of decedents and subjects who had moved, and deletion of ineligible participants

To confirm if study participants had survived and were living in the study area at the end of follow-up, we conducted a systematic review of population registers of cohort members in 17 areas followed until 2009. In the remaining 18 areas followed until 2009, annual or biannual follow-up surveys were routinely performed using population registers; thus, no further reviews were conducted. If data from participants presumed to survive were found to be missing at the end of 2009, attempts were made to obtain information on their mortality status or current location, and relevant information was added to the follow-up data. A few participants were found to have never lived in the study area and were thus excluded from the baseline data.

This review process revealed some errors in coding of date of birth and sex. Moreover, during the merge of follow-up data with baseline identifiable data (name, date of birth, and sex), further errors in date of birth and sex were found. All such errors were corrected.

RESULTS

Of 110 792 participants aged 40 to 79 years at baseline, 207 (0.19%) were found to have never lived in the study area. As a result, 110 585 participants (46 395 men and 64 190 women) were ultimately deemed eligible as subjects for the JACC Study, with 707 136 and 1 025 703 person-years of follow-up for men and women, respectively. Errors in the coding of date of birth and sex were found in 356 (0.32%) and 59 (0.05%) cases, respectively, during routine follow-up and final review. Table 1 shows the age and sex distribution of study participants. There were no subjects from the Shikoku region. As compared with the overall distribution of the Japanese population in 1989, our cohort participants were slightly older and included a higher percentage of women.

Table 2 shows the follow-up results, and Table 3 shows the major causes of death up to 2009. These values include the follow-up information (death or move-out from the study area) that was reported in 10 of 17 areas for 516 subjects (0.5%) through a systematic review of population registers of cohort members. Finally, 27 410 deaths (24.8%; 15 401 men, 12 009 women) and 6402 move-outs (5.8%; 2343 men, 4059 women) were identified during the median 18.0-year follow-up. The first cause of death was cancer among men (37.6%) and circulatory disease among women (33.7%), and the second cause of death was circulatory disease (27.8%) and cancer (30.8%), respectively (Table 3). Among those who died of cancer, the first, second, and third leading causes of death were cancer of the lung (23.2%), stomach (18.4%), and liver (10.7%) among men and cancer of the stomach (15.4%), lung (11.2%), liver, and pancreas (9.2% for both)

Table 1. Age distribution of cohort members at baseline by region

	Age at baseline								Total	%
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79		
Men										
Japan general population 1989 (×1000)	5022	4562	3967	3706	3122	2049	1507	1169	25 104	
	20.0	18.2	15.8	14.8	12.4	8.2	6.0	4.7	100.0	
JACC Study participants	5991	5794	6309	7690	8415	5516	4021	2659	46 395	100.0
%	12.9	12.5	13.6	16.6	18.1	11.9	8.7	5.7	100.0	
Hokkaido	191	182	211	267	284	201	86	43	1465	3.2
Tohoku	809	625	797	1050	1270	894	494	293	6232	13.4
Kanto	1325	1231	1219	1320	1446	1115	707	447	8810	19.0
Chubu	1736	1646	1560	1763	1804	1167	916	691	11 283	24.3
Kinki	960	908	1148	1456	1419	996	651	459	7997	17.2
Chugoku	220	374	452	886	1251	589	770	509	5051	10.9
Kyushu	750	828	922	948	941	554	397	217	5557	12.0
Women										
Japan general population 1989 (×1000)	4989	4613	4052	3852	3426	2825	2141	1770	27 668	
	18.0	16.7	14.6	13.9	12.4	10.2	7.7	6.4	100.0	
JACC Study participants	7536	7912	9088	10 792	11 102	8589	5548	3623	64 190	100.0
%	11.7	12.3	14.2	16.8	17.3	13.4	8.6	5.6	100.0	
Hokkaido	310	310	433	436	382	257	93	37	2258	3.5
Tohoku	959	963	1412	1670	1670	1136	604	372	8786	13.7
Kanto	1428	1438	1442	1605	1744	1577	892	542	10 668	16.6
Chubu	1872	1669	1833	1933	2107	1613	1225	882	13 134	20.5
Kinki	1253	1219	1508	1784	1566	1300	876	623	10 129	15.8
Chugoku	300	796	828	1479	2194	1795	1289	844	9525	14.8
Kyushu	1414	1517	1632	1885	1439	911	569	323	9690	15.1

Table 2. Follow-up status until 2009 by sex and age

	Age at baseline								Total
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	
Men									
No. at baseline	5991	5794	6309	7690	8415	5516	4021	2659	46 395
No. of deaths	394	658	1113	2000	3252	3056	2782	2146	15 401
%	6.6	11.4	17.6	26.0	38.6	55.4	69.2	80.7	33.2
No. who left study area	539	377	303	298	292	242	180	112	2343
%	9.0	6.5	4.8	3.9	3.5	4.4	4.5	4.2	5.1
Person-years	107 048	102 338	108 465	124 421	123 896	74 267	43 689	23 012	707 136
Mortality rate (per 1000 person-years)	3.7	6.4	10.3	16.1	26.2	41.1	63.7	93.3	21.8
Women									
No. at baseline	7536	7912	9088	10 792	11 102	8589	5548	3623	64 190
No. of deaths	242	368	637	1218	1982	2544	2632	2386	12 009
%	3.2	4.7	7.0	11.3	17.9	29.6	47.4	65.9	18.7
No. who left study area	605	488	479	522	606	592	483	284	4059
%	8.0	6.2	5.3	4.8	5.5	6.9	8.7	7.8	6.3
Person-years	134 927	139 091	159 465	182 347	174 721	125 510	71 076	38 566	1 025 703
Mortality rate (per 1000 person-years)	1.8	2.6	4.0	6.7	11.3	20.3	37.0	61.9	11.7

among women. When cancers of the colon and rectum were grouped together, that category was the second leading cause of death (12.7%) among women.

DISCUSSION

This final profile of the JACC Study Group describes the number of participants and their follow-up status. During the median 18-year follow-up, we found errors in the coding of date of birth and sex data as well as incorrectly registered cases. Accordingly, we would advise future researchers planning a field study to thoroughly check participant eligibility and basic information such as date of birth and sex; this can be performed at least twice, by using a population register and a self-questionnaire.

Although follow-up information was annually or biannually confirmed, 516 subjects who had died or moved out of the study area were not identified during routine follow-up. The

Table 3. Mortality distribution according to cause of death during entire follow-up period

Cause of death		Men											Women										
		Age at baseline								Total	%	%[a]	Age at baseline								Total	%	%[a]
		40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79				40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79			
All causes		394	658	1113	2000	3252	3056	2782	2146	15401	100.0		242	368	637	1218	1982	2544	2632	2386	12009	100.0	
A00–B99	Certain infectious and parasitic diseases	6	10	18	38	56	62	44	33	267	1.7		4	4	18	31	62	50	43	36	248	2.1	
C00–D49	Neoplasms	160	312	542	927	1425	1073	792	561	5792	37.6	100.0	147	182	319	563	740	714	618	414	3697	30.8	100.0
C15	Esophagus	12	14	28	42	55	38	17	10	216		3.7	0	1	5	3	4	7	8	7	35		0.9
C16	Stomach	32	62	87	176	252	199	151	109	1068		18.4	19	26	33	93	91	127	104	76	569		15.4
C18	Colon	12	14	36	41	67	59	44	35	308		5.3	2	13	29	45	62	65	65	52	333		9.0
C19–C20	Rectum	8	17	26	52	39	30	27	22	221		3.8	9	8	12	18	35	16	26	11	135		3.7
C22	Liver and intrahepatic bile ducts	21	46	79	128	167	77	66	37	621		10.7	8	12	29	65	81	77	33	35	340		9.2
C23	Gall bladder	1	5	6	16	17	32	12	12	101		1.7	4	7	11	15	17	28	35	13	130		3.5
C24	Other and unspecified parts of biliary tract	5	11	11	34	41	42	28	16	188		3.2	3	8	11	22	31	37	37	23	172		4.7
C25	Pancreas	13	20	29	50	78	63	43	42	338		5.8	7	16	26	48	82	66	62	33	340		9.2
C33–C34	Lung	27	50	114	205	364	290	181	114	1345		23.2	18	20	39	54	96	78	70	40	415		11.2
C50	Breast	0	1	0	0	0	0	1	0	2		0.0	28	26	28	37	29	18	17	9	192		5.2
C53	Cervic uteri												6	2	10	5	9	5	7	5	49		1.3
C54	Corpus uteri												2	2	7	7	9	3	4	2	36		1.0
C55	Uterus, part unspecified												2	3	1	3	13	9	8	7	46		1.2
C56	Ovary												13	8	15	16	22	10	9	5	98		2.7
C61	Prostate	2	4	20	21	68	49	59	56	279		4.8											
C64	Kidney	0	4	7	12	14	9	12	4	62		1.1	0	0	1	5	3	11	5	1	26		0.7
C65–C67	Urothelial tract	2	7	13	11	40	31	34	17	155		2.7	1	0	6	6	21	14	16	14	78		2.1
C82–C85	Non-Hodgkin's lymphoma	0	8	17	29	44	20	15	15	148		2.6	5	6	10	25	23	17	12	7	105		2.8
C90	Multiple myeloma	2	7	4	12	18	12	9	5	69		1.2	4	4	9	12	15	15	11	10	80		2.2
C92	Myeloid leukemia	5	10	11	16	17	7	9	3	78		1.3	1	4	4	12	15	9	8	3	56		1.5
E00–E89	Endocrine, nutritional and metabolic diseases	8	10	17	29	38	35	27	28	192	1.2		2	4	7	10	36	49	48	43	199	1.7	
G00–G99	Diseases of the nervous system	4	7	17	19	50	39	18	10	164	1.1		1	4	12	23	44	27	29	13	153	1.3	
I00–I99	Diseases of the circulatory system	86	132	252	460	857	908	919	673	4287	27.8		52	70	138	306	585	913	1001	978	4043	33.7	
I20–I25	Ischemic heart disease	34	45	69	124	199	204	181	147	1003			11	8	34	51	105	188	176	185	758		
I48	Atrial fibrillation and flutter	0	0	4	10	19	25	24	15	97			1	0	1	3	16	21	29	26	97		
I50	Heart failure	7	19	26	56	121	151	178	153	711			8	5	22	44	101	180	200	239	799		
I60–I69	Cerebrovascular disease	30	44	113	194	362	389	408	285	1825			24	43	63	130	256	393	461	407	1777		
I71	Aortic aneurysm and dissection	4	4	12	21	44	40	38	15	178			2	3	2	17	22	29	28	13	116		
J00–J99	Diseases of the respiratory system	14	40	62	219	408	501	550	500	2294	14.9		3	18	23	67	182	281	357	354	1285	10.7	
J09–J18	Influenza and pneumonia	6	20	30	115	228	273	327	327	1326			2	11	15	39	110	173	247	245	842		
J43	Emphysema	0	1	6	19	58	58	64	44	250			0	0	0	2	2	4	4	4	16		
K00–K95	Diseases of the digestive system	28	35	53	78	82	109	80	46	511	3.3		1	12	13	54	54	106	91	82	413	3.4	
K74	Fibrosis and cirrhosis of liver	16	16	27	34	20	13	19	6	151			1	8	6	23	22	31	19	10	120		
N00–N99	Diseases of the genitourinary system	2	9	14	33	67	68	67	59	319	2.1		2	3	15	22	51	78	82	81	334	2.8	
N17–N19	Acute kidney failure and chronic kidney disease	2	7	12	22	50	52	52	53	250			1	2	12	17	38	50	63	60	243		
R00–R99	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	4	4	6	7	26	52	99	109	307	2.0		1	1	1	7	26	84	172	234	526	4.4	
R54	Age-related physical debility	0	0	0	4	19	37	87	99	246			0	0	1	2	18	71	150	224	466		
S00–T88	External causes	78	86	113	150	170	150	126	93	966	6.3		22	57	72	97	143	147	117	73	728	6.1	
	Others	4	13	19	40	73	59	60	34	302	2.0		7	13	19	38	59	95	74	78	383	3.2	

[a]Percentage of deaths per neoplasm.

use of population registers to verify that subjects are living in the study area is therefore necessary because it enables identification of deceased individuals and those who have moved out of the study area. Furthermore, 356 (0.32%) and 59 (0.05%) cases of incorrect coding of date of birth and sex, respectively, were found during routine follow-up and final review. Miscoding of data can occur by verification only once, and miscoding of date of birth and sex information may cause errors such as merging of the follow-up information of 1 participant with the baseline data of another participant. Thus, careful efforts such as independent double-entry are essential to reduce such miscoding.

The JACC Study is one of the largest cohort studies in Japan. Selected characteristics of study participants were similar to those of the Japanese general population, and thus, the JACC Study can be regarded as representative of the Japanese population, though it should be noted that no subjects were recruited from the Shikoku region. Almost 200 original articles on the risk factors for cancer, cardiovascular disease, and other diseases have been published using the results of the JACC Study. It was not an easy task to establish and maintain such a large collaborative cohort study with a limited budget; the voluntary efforts of the collaborators were essential. Although unexpected errors were found, we believe that the impact of these errors was negligible because the number of ineligible cases and amount of missing data were small relative to the large total study population.

Cohort studies need to continue over a long period if they are to yield fruitful results. Moreover, because all study participants must be followed up carefully and thoroughly, considerable funding is required. The JACC Study received systematic support for the first 10 years, at which point this funding ceased and maintenance and follow-up of cohort participants was accomplished by means of smaller grants. The retirements of principal researchers and city mergers throughout Japan made it difficult to continue follow-up. Thus, we decided to terminate the follow-up of participants in the JACC Study at the end of 2009. Our experience indicates that the development and maintenance of an appropriate long-term management system is essential when launching a cohort study and that adequate and steady support from funding bodies is also important.

We would like to express our sincere thanks to all participants and researchers related to the JACC Study, and to all the funding bodies that supported our study. Hereafter, we plan to use the final dataset and remaining sera to examine the risk impact of lifestyle factors and levels of serum components on human health.

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Conflicts of interest: None declared.

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