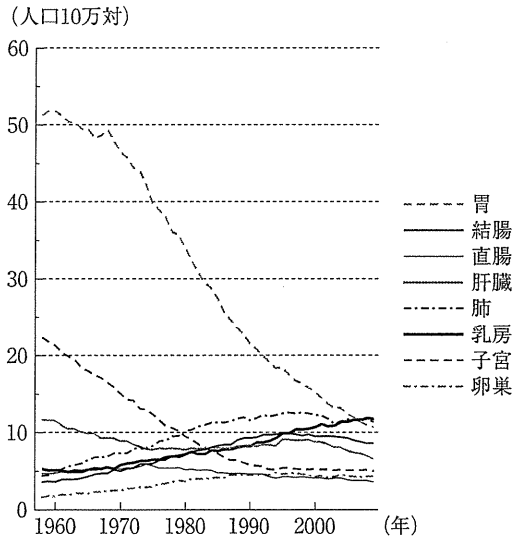

図1 部位別がん年齢調整死亡率の推移（主要部位）
（女性 1958–2009年）
資料：独立行政法人国立がん研究センターがん対策情報センター（Center for Cancer Control and Information Services, National Cancer Center, Japan）

階級別の年次推移をみると，50歳代後半以降の死亡率の増加が特に大きくなっている（**図3**）．

欧米諸国の乳がん年齢調整死亡率は，日本に比べかなり高い．しかしながら，1990年あたりをピークに減少傾向が始まっており，日本との差は縮まる傾向にある（‘乳癌の疫学—国際比較—’の稿にて詳説）．

2 乳がん罹患率

1）統計情報の入手方法

我が国では，死亡と異なり，がん罹患率や生存率など，罹患に関するデータを国として系統的に把握する仕組みがない．罹患率を推定するためには，ある集団を設定し，その集団で一定期間に発生した罹患数を把握する必要があり，これを実現するためには地域がん登録が不可欠である．地域がん登録は，がん対策の立案と評価や，がん医療の向上のために世界の多くの国や地域で行われており，日本では，1950年代に宮城県，広島市，長崎市で開始された．ついで1960年代に大阪府，愛知県などで始められ，2011年11月時点で，日本では45道府県および1市で地域がん登録事業が実施されている．

我が国では，全国規模での地域がん登録が行われていないため，一定の精度基準を満たした10数県の地域がん登録のデータに基づき，全国推計値を算出することで国レベルのがんの罹患状況を把握している．1975–94年の全国がん罹患推定は，厚生労働省がん研究助成金による「地域がん登録精度向上と活用に関する研究」班が，1995年以降の推計は，厚生労働科学研究費補助金第3次対がん総合戦略研究事業「がん罹患・死亡動向の実態把握の研究」班で罹患データを集計し，国立がん研究センターがん対策情報センターで報告書としてまとめて公表を行っている．集計結果は，前述のがん情報サービスホームページの集計表のダウンロードで公開されている[1]．各地域からのデータ提出と集計作業に時間がかかるため，公表時期は罹患年より5–6年遅れとなっている．2012年1月現在，全国がん罹患推計の最新年は2006年である．

2）粗罹患率と年齢調整罹患率

罹患率についても，死亡率と同様に，一定期間の罹患数（推計による）を単純にその期間の人口で割った粗罹患率と，集団全体の罹患率を基準となる集団の年齢構成（基準人口）に合わせた年齢調整罹患率とが用いられる．

3）乳がん罹患率の動向

がん年齢調整罹患率の推移をみると，全がんでは男女とも1990年代前半までは増加し，その後は横ばいで，2000年前後から再び増加傾向にある．男性では胃がん，肝臓がんなどで近年減少傾向がみられるが，直腸がん，前立腺がんなどは増加傾向にある．女性では，胃がん，肝臓がんなどで近年減少傾向がみられるが，乳がん，卵巣がん，肺がんなどで増加傾向にあり，特に乳がんと卵巣がんは1975年から一貫した増加傾向が続いている（**図2，4**）．

女性のがんの年齢調整罹患率は，2006年の推計によると，乳がんが最も高く人口10万対65.6であり，2番目に高い大腸がん（直腸と結腸を合わせたもの）の36.4と比べても圧倒的に高い罹患率となっており，2006年の推計では，

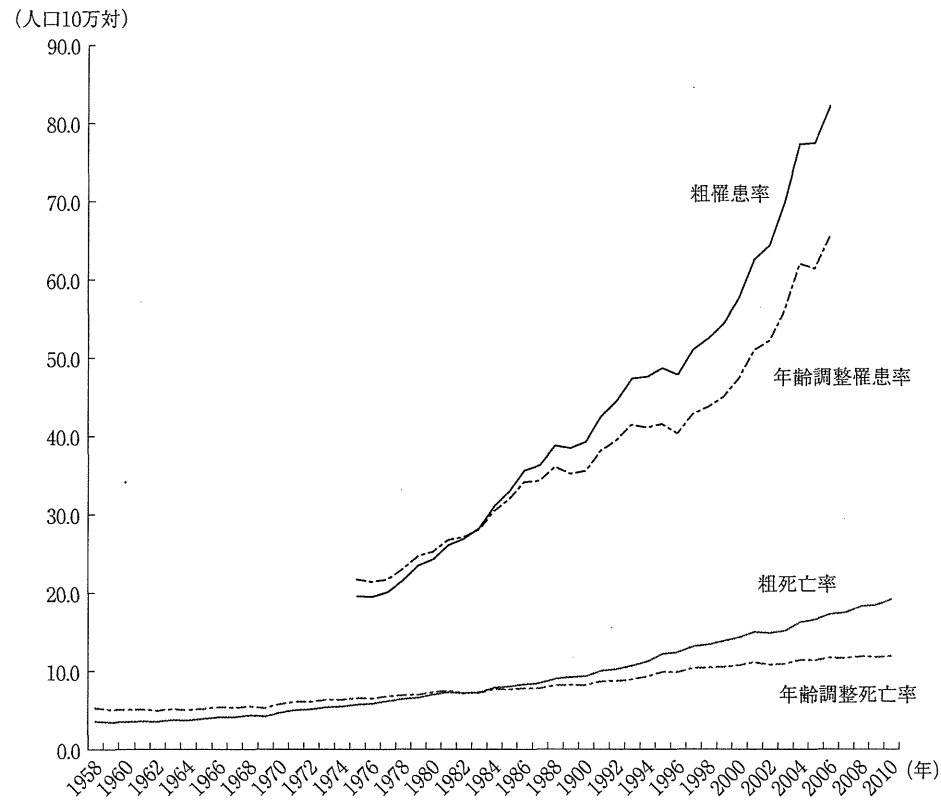

図2 乳がん死亡率および罹患率の年次推移

資料：独立行政法人国立がん研究センターがん対策情報センター(データをもとに著者が作成)

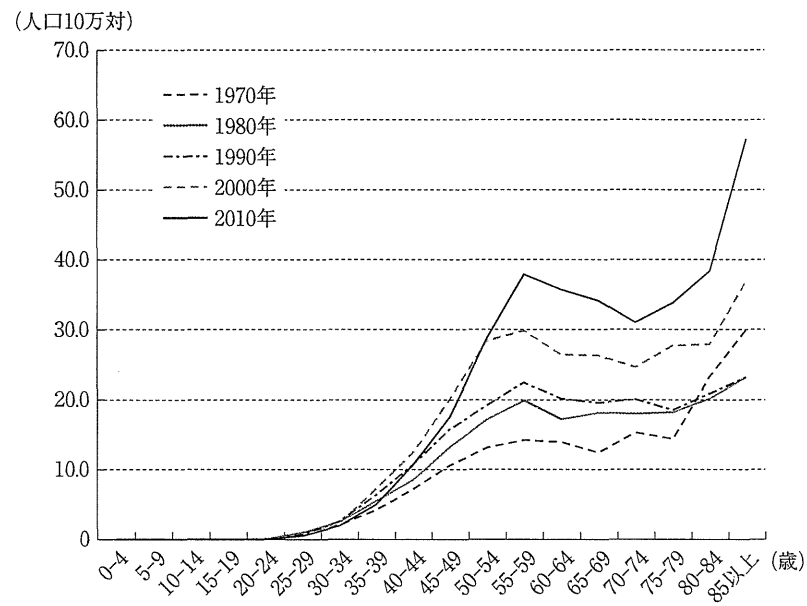

図3 年齢階級別乳がん粗死亡率の推移

資料：独立行政法人国立がん研究センターがん対策情報センター(データをもとに著者が作成)

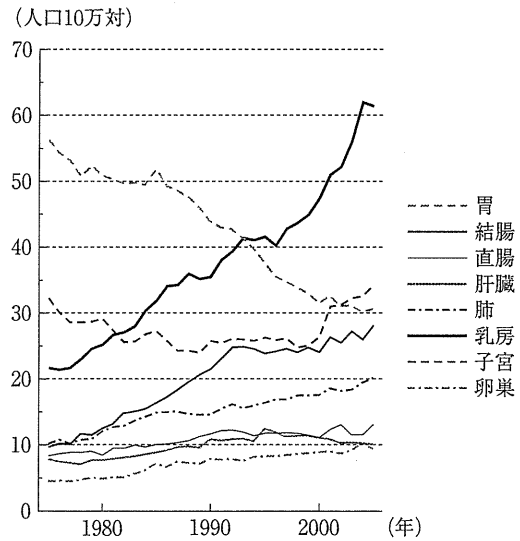

図4　部位別がん年齢調整罹患率の推移（主要部位）
（女性 1975–2005年）
資料：独立行政法人国立がん研究センターがん対策情報センター
（Center for Cancer Control and Information Services, National Cancer Center, Japan）

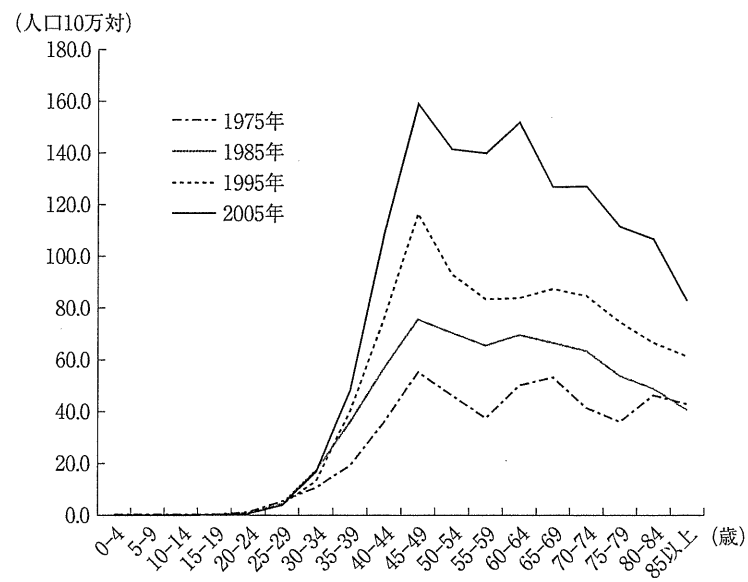

図5　年齢階級別乳がん粗罹患率の推移
資料：独立行政法人国立がん研究センターがん対策情報センター
（データをもとに著者が作成）

53,783人が罹患している．年齢階級別にみた女性の乳がんの罹患率は30歳代から増加しはじめ，40歳代にピークを迎え，その後は次第に減少する(**図5**)．また年齢階級別に罹患率の推移をみると，すべての年代で罹患率が大きく増加しており，特に40歳代から50歳代で増加の割合が大きくなっている(**図5**)．

おわりに

これまでみてきたように，我が国における乳がんの動向は，罹患数，死亡数ともにいまだ一貫した増加傾向にある．

乳がん検診については，40歳以上の女性全員に対してマンモグラフィが推奨されている．しかし，国民生活基礎調査に基づく国立がん研究センターがん対策情報センターの推計によると，2010年の乳がん検診受診率は24.3％であり，2007年のがん対策推進基本計画の個別目標であるがん検診受診率50％以上の半分にも満たない[1]．早期発見による乳がん死亡率減少のために，推奨に基づいた乳がん検診を全員が受診することが重要である．

また，乳がん危険因子として，乳がん家族歴やBRCA1，BRCA2遺伝子などの遺伝的素因，初経や閉経に関する内分泌環境因子，出産や授乳など社会環境とともに，生活環境要因として，肥満や身体活動，アルコール摂取などが明らかになっている．生活環境要因は，自ら行動変容できる要因であるため，予防に用いることが可能である．十分なエビデンスがあるものは多くはないが，まずは利用可能なエビデンスの中から，他の疾患への影響も含め，リスクとベネフィットを考慮して予防行動につなげていくことが必要である．

乳がんの増加に早急に対応するために，現状での最善策として，国民ひとりひとりが乳がんのリスクを知り，それぞれが予防行動をとるとともに，推奨に基づいた乳がん検診を受診すること，そしてその普及も含め，個人の行動の実践を社会が支援していくことが重要である．

文献

1) http://ganjoho.jp/professional/statistics/index.html; Accessed January 24, 2012.

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ORIGINAL ARTICLE

Validity and applicability of a simple questionnaire for the estimation of total and domain-specific physical activity

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Abstract
Purpose We developed and evaluated a simple, robust and valid self-administered questionnaire for the estimation of physical activity (PA). Here, we examined the validity of this questionnaire in subjects with differing sex, ages, occupations and living circumstances.
Methods The questionnaire consists of four domains, namely occupational activity, including housekeeping and commuting; leisure time activity; sleeping; and other activities. It was validated with 8-day, 24-h physical activity records (24 h-R) as the gold standard in 110 volunteers.
Results Total PA estimated by the questionnaire and the 24 h-R showed a moderately strong correlation ($r = 0.69$). Correlations between total PA by the PAQ and the 24 h-R for various subgroups, such as sex, age, area, occupation and BMI, were moderate to strong (0.55–0.80). Validity of domain-specific PA calculated by the questionnaire was also moderate to high.
Conclusion This simple questionnaire produces valid estimates of total and domain-specific PA and can be applied to a broad population.

Keywords Physical activity questionnaire · Physical activity · Epidemiology · Validity · 24-h Physical activity record

On behalf of the JPHC Study Group.

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Introduction

Interest in the association between daily physical activity (PA) and the development of chronic diseases, such as diabetes [1–4], ischemic heart disease [5, 6] and cancers [7], has increased. This in turn has led to a need to quantify the effective threshold of activity [8], qualify varying physical activities and determine whether disease prevention is better discussed in terms of vigorous or moderate activity, or leisure time activity or occupational activity.

For practical reasons, large-scale epidemiological studies usually measure physical activity using a physical activity questionnaire (PAQ) not using more precise measurements, such as doubly labeled water or physical activity records. Moreover, because whole questionnaires used in epidemiological studies devote relatively little time and space to physical activity, the PAQ component must be short and accurate. This in turn hampers the development of PAQs that can estimate PA in different target

populations (e.g., by gender, age, occupation, geographical location, environment, etc.). Accordingly, many of the PAQs reported to date were developed for use in specific populations, such as nurses [5], physicians [9], office workers [10–12] and college alumni [7, 13], which tend to be homogenous in terms of both background and physical activity pattern. Given the difficulty in asking about overall activity, previous PAQs focused mostly on specific activities, such as leisure time, or moderate or vigorous activity, rather than total PA.

We therefore sought to develop a simple, robust and valid PAQ capable of measuring physical activity in a range of subjects, such as people living in both urban and rural areas, or subtropical to cold or snowy places. The aim of the PAQ is to be used in epidemiological studies for ranking individuals by PA adjusted with body size rather than estimating energy expenditure. Further, we sought to measure total PA as well as PAs for specific activities, such as at leisure and occupation, and for specific intensity, such as moderate or vigorous activities. In addition, because physical activity may differ among seasons, validity may be affected if the answer to the PAQ depends on when it is administered. We therefore aimed at measuring year-round average physical activity regardless of when the PAQ is administered.

Here, we developed and validated a PAQ in a Japanese cohort study against 24-h physical activity records (24 h-R).

Methods

The JPHC Study

The questionnaire was originally developed and used in the Japan Public Health Center-based prospective Study (JPHC Study) [14], a prospective follow-up study conducted widely throughout Japan that investigated mainly cancer and cardiovascular diseases. Cohort I was begun in 1990 and enrolled 61,595 subjects (29,980 men and 31,615 women) in four population cohorts and one health-checkup cohort, while Cohort II was begun in 1993 and enrolled an additional 78,825 residents (38,740 men and 40,085 women) in five population-based and one health-checkup cohort.

Subjects of the validation study

These subjects represented a subsample of participants in specific geographic areas covered by four public health centers (PHC) of the JPHC Study.

A total of 110 subjects (54 males and 56 females; 20 from the Katsushika PHC area of Tokyo, 38 from the Miyako PHC area of Okinawa Prefecture, 30 from the Saku PHC area of Nagano Prefecture and 22 from the Kashiwazaki PHC area of Niigata Prefecture) were recruited from both cohorts in an attempt to include urban areas as well as rural agricultural areas that cultivated rice, apples, sugarcane, etc. We also wanted to include subjects from both the western and eastern parts of Japan, and both cold and subtropical areas.

We selected married couples in their 50s or 60s for convenience and requested their voluntary participation. Approval for the study was obtained from the Institutional Review Board of the National Cancer Center, and written informed consent was obtained from the subjects.

The PAQ in the JPHC Study

The PAQ questionnaire, which was originally developed as part of the 10-year follow-up questionnaire survey used in the JPHC Study, was constructed based on the simple notion that total daily energy expenditure consists of four domains, namely occupational activity, including housekeeping and commuting; leisure time activity; sleeping; and other activities (Appendix). The questionnaire is intended to estimate habitual total and domain-specific physical activity in metabolic equivalent (MET) (kcal/kg/h)-hours per day averaged over 1 year. Subjects were asked about their activities in each of these domains during the preceding year. With regard to occupational activity, they were asked about the number of hours spent at different levels of intensity (sitting, standing, walking, strenuous work); and for leisure time activity about the frequency and number of hours spent at different levels of intensity (walking slowly, walking quickly, light to moderate and strenuous exercise). A question about sleeping hours was also asked, and then hours for other activities were calculated as the difference between the sum of the other three activities and 24 h. Total PA was calculated as the sum of hours spent for the respective activity multiplied by METs, namely 1.5, 2, 2, 4.5 and 0.9 for sitting, standing, walking, strenuous work and sleeping, respectively, for occupational activities and sleeping; and 3, 4, 4 and 4.5 for walking slowly, walking quickly, light to moderate exercise and strenuous exercise, respectively, for leisure time activities. Intensity for "other activities" was considered the same as that for sitting, at 1.5. This estimation method is referred to below as "PA without seasonal variation."

To take account of seasonal differences in activities, the PAQ also asked several questions concerning working hours and duration in months in busier seasons. The seasonally adjusted total PA was calculated as the weighted mean of the total PA for the normal season and that for the busy season, for which PA for occupational activities was multiplied by the ratio of working hours in the busy season to the normal season. This estimation method is referred to below as "PA with seasonal variation."

Study design

The subjects were asked twice about their physical activities in different seasons, one time during the main harvest season (if present) and the other time in a different season for each study area (Fig. 1). The PAQ and 24 h-R were used in each season over a study period of 9 days. On the first day, each participant was asked to complete the PAQ, then given instructions on the study procedure and filled out the 24 h-R on 4 days. On day 9, the 24 h-Rs were collected and checked. Below, the PAQs conducted in the first survey are denoted as PAQ1 and those in the second survey as PAQ2.

The 24-h physical activity record

The participants were asked to complete a 24 h-R based on the form of Bouchard [15], modified by Naito et al. [12], by recording activity for each 15-min interval. They were instructed to record their activities in as much detail as possible for 4 days each for two seasons, which were to include one Sunday or other day off plus three ordinary work days.

The data were converted into MET-hour values based on a compendium of physical activities [16] and simply averaged over 8 days to estimate habitual daily physical activity. These MET-hour values were used as the gold standard to assess the validity of the PAQ estimates [13, 17].

Statistical analysis

Validity of the PAQ was determined by comparing total PA estimated by the PAQ (PA with and without seasonal variation) to that by the 24 h-R as gold standard. Comparisons were made using Spearman's correlation coefficients with 95% confidence intervals (CIs). To examine reproducibility, the MET-hours estimated by the two PAQs administered in the different seasons were compared. In addition, to evaluate the broad applicability of the PAQ, correlation coefficients with the 24 h-R were calculated by sex, area, age group, occupation and body mass index (BMI). Four domain-specific PAs were also evaluated for validity.

All analyses were performed using JMP Software (version 6. SAS Institute Inc., 2005).

Results

Characteristics and daily total PA of the study participants

Data were analyzed for 110 subjects who participated in two surveys. Mean age was 60.7 years, and mean BMI was 24.2. Although we recruited people in their 50s and 60s, two spouses in their 40s and nine in their 70s were included in the analyses.

Daily total PA calculated with the 24 h-R by subgroup is shown in Table 1. There were statistically significant differences in occupation, but not in sex, age group, area or BMI. For descriptive purposes, seasonal difference was also examined. There were seasonal variations between two surveys, which mainly came from the difference in agricultural area, such as Saku and Kashiwazaki.

Validity and reproducibility of the PAQ

With regard to the 24 h-R, Spearman's correlation coefficients were 0.69 (95% CI 0.57–0.77) for PAQ1 without seasonal variation, 0.68 (95% CI 0.57–0.77) for PAQ1 with seasonal variation, 0.55 (95% CI 0.43–0.70) for the PAQ2 without seasonal variation, and 0.58 (95% CI 0.43–0.70) for the PAQ2 with seasonal variation.

Total PA calculated with the PAQ tended to underestimate those with the 24 h-R. While correlation coefficients with the 24 h-R were almost the same for the PAQ with and without seasonal variation, calculated METs tended to be a little larger for the PAQ with seasonal variation than without seasonal variation (Table 2). As for reproducibility, correlations between the two PAQs were 0.68 (95% CI 0.56–0.77) without and 0.68 (95% CI 0.57–0.78) with seasonal variation.

Validity by different subgroups

Physical activity estimated by the 24 h-R for various subgroups is shown in Table 3. Variations were observed by

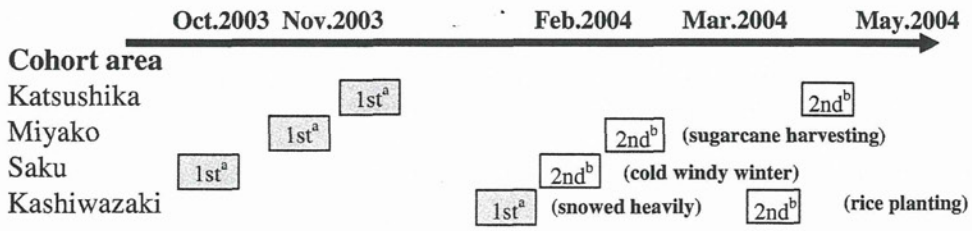

Fig. 1 Design of the validation study. *a* First survey, *b* second survey

Table 1 Daily total physical activity in MET-hours calculated from the 24 h-R by subgroup

Characteristics	Mean daily PA for 1st and 2nd 24 h-R surveys							Mean daily PA for 24 h-R1			Mean daily PA for 24 h-R2			
	n	Min	Med	Max	Mean	SD	p^a	*n*	Mean	SD	*n*	Mean	SD	p^b
All subjects	110	31.1	40.1	63.6	40.3	4.87	–	107	39.9	4.75	103	40.6	5.99	0.04
Sex														
Male	54	31.1	39.6	63.6	39.7	5.63	0.22	52	39.2	5.53	51	40.0	6.68	0.09
Female	56	33.8	40.5	57.3	40.8	3.97		55	40.5	3.81	52	41.1	5.24	0.25
Age group														
50	46	31.1	39.9	50.6	39.5	4.39	0.19	43	39.2	4.61	42	39.8	5.18	0.22
60	55	32.2	40.3	57.3	40.5	4.24		55	40.0	4.18	52	40.8	5.29	0.12
70	9	31.7	41.3	63.6	42.6	9.12		9	42.0	7.85	9	43.2	11.41	0.63
Area														
Katsushika	20	32.2	40.2	46.3	39.4	3.82	0.52	20	39.0	4.25	20	39.8	4.18	0.35
Miyako	38	31.1	39.7	63.6	41.1	6.50		37	40.5	5.86	31	41.4	8.42	0.17
Saku	30	31.5	40.0	46.9	39.6	3.51		28	40.8	3.78	30	38.6	3.50	0.00
Kashiwazaki	22	31.7	41.3	45.7	40.5	3.97		22	38.2	3.83	22	42.8	5.32	0.00
Occupation														
Clerk	17	31.1	37.4	50.6	37.7	4.80	0.00	17	37.5	5.09	14	36.9	3.74	0.59
Shopkeeper, sales	43	31.5	39.6	47.9	39.6	3.42		40	38.7	3.63	43	40.6	4.55	0.01
Housewife, light activity	20	32.6	40.0	47.6	39.6	4.35		20	39.8	4.45	18	39.5	4.98	0.57
Agriculture	30	36.1	41.9	63.6	43.1	5.80		30	42.8	4.85	28	43.1	8.16	0.56
BMI														
Less than 22	25	31.7	42.1	50.6	41.2	4.78	0.53	25	40.6	5.09	22	40.8	5.02	0.20
22–25	47	31.5	39.6	57.3	39.8	4.57		44	39.7	4.37	45	40.2	5.75	0.40
More than 25	38	31.1	39.8	63.6	40.2	5.30		38	39.5	5.01	36	41.0	6.90	0.16

METs Metabolic equivalents, *24 h-R1* 24-h physical activity record 1st survey, *24 h-R2* 24-h physical activity record 2nd survey

[a] *p* Values by ANOVA comparing mean daily PA within each characteristics

[b] *p* Values by paired t test comparing mean daily PA between 24 h-R1 and 24 h-R2

Table 2 Daily total physical activity (MET-hours) calculated from 24-h physical activity record and physical activity questionnaire

All subjects	*n*	Min	Med	Max	Mean	SD
24-h Physical activity record	110	31.1	40.1	63.6	40.3	4.87
PAQ1 (without[a])	109	27.3	37.0	57.4	38.2	6.07
PAQ1 (with[b])	109	27.3	37.4	57.6	38.4	6.16
PAQ2 (without[a])	105	26.9	36.2	56.4	37.3	6.00
PAQ2 (with[b])	105	26.9	36.3	59.6	37.6	6.31

PAQ Physical activity questionnaire, *PAQ1* first survey, *PAQ2* second survey

[a] Without seasonal variation

[b] With seasonal variation

sex, age group, area, occupation and BMI, although not necessarily with significance. Consistently high correlations were observed between the 24 h-R and PAQ both with and without seasonal variation for most of the subgroups (Table 3). Correlation coefficients by the PAQ with and without seasonal variation are virtually same (data not shown).

Distribution of PA among domains

The four domain-specific PAs are shown in Table 4. For total PA, occupational activity and other activities each contributed more than one-third of the total. With regard to the correlations between domain-specific PA from PAQ1 without seasonal variation and those from 24 h-R, high correlation was observed for sleeping, and moderate correlations were observed for occupational activity and leisure time physical activity. In contrast, a low correlation was observed for other activities. Further, domain-specific correlation was not improved when seasonal variation was taken into account. The results for PAQ2 were similar to those for PAQ1 (data not shown).

Table 3 Correlation coefficients of the physical activity questionnaire and 24-h physical activity record by subgroup

Characteristics	PAQ1			
	Without[a]		With[b]	
	r^c	95%CI	r^c	95%CI
All subjects	0.69	0.57–0.77	0.68	0.57–0.77
Sex				
Male	0.80	0.68–0.88	0.80	0.68–0.88
Female	0.58	0.37–0.73	0.57	0.36–0.73
Age group				
50	0.76	0.61–0.86	0.77	0.62–0.87
60	0.59	0.39–0.74	0.60	0.40–0.74
70	0.80	0.29–0.96	0.78	0.25–0.95
Area				
Katsushika	0.76	0.47–0.90	0.76	0.47–0.90
Miyako	0.72	0.52–0.85	0.73	0.53–0.85
Saku	0.55	0.22–0.76	0.58	0.27–0.78
Kashiwazaki	0.68	0.36–0.86	0.60	0.24–0.82
Occupation				
Clerk	0.73	0.39–0.90	0.65	0.25–0.86
Shopkeeper, sales	0.65	0.43–0.79	0.65	0.44–0.80
Housewife, light activity	0.57	0.18–0.81	0.58	0.19–0.82
Agriculture	0.74	0.52–0.87	0.75	0.53–0.88
BMI				
Less than 22	0.72	0.46–0.87	0.71	0.43–0.86
22–25	0.58	0.35–0.75	0.58	0.35–0.75
More than 25	0.69	0.48–0.83	0.70	0.49–0.83

PAQ Physical activity questionnaire, *PAQ1* first survey

[a] Without seasonal variation

[b] With seasonal variation

[c] Spearman's correlation coefficient

Discussion

This study demonstrates the validity and reproducibility of the PAQ used in the JPHC study. Further, the validity of the PAQ answers for the estimation of average physical activity over 1 year was confirmed against the possibe seasonal variation in PA even within rural agricultural areas. In addition, the validity of the PAQ was also confirmed for various subgroups defined by sex, age, area of residence, occupation and BMI.

Reflecting the subjects of the JPHC study, our present subjects came from widely varying areas of Japan and occupations. The age category of the 50s and above was selected to reflect the JPHC study's purpose, namely to study the onset of diseases such as cancer, diabetes and cardiovascular disease. Despite the wide variation among subjects, our simple PAQ showed good validity, with a higher correlation with 24 h-R PA values ($r = 0.55$–0.80) than in a study on female alumnae ($r = 0.15$–0.52) (Historical Leisure Activity Questionnaire) [13].

The results from the 24 h-R in this study showed the presence of a seasonal difference in PA, especially in agricultural areas and among farm laborers. An increase in PA during the 'busy season' came from farm work such as harvesting, while a relative decrease in PA during other seasons resulted from environmental factors such as hot summers and cold winters, including snowfall-related sedentariness, resulting in seasonal differences. Thirty of our subjects described themselves as farmers, but a number of others also farmed as a side job, and some housewives in rural areas also farmed. The first survey in the Kashiwazaki area was conducted

Table 4 Domain-specific physical activity and their correlations between 24-h physical activity record and physical activity questionnaire

	Total PA (METs) by 24 h-R		Domain-specific PA by PAQ1 (without[a]) versus domain-specific PA by 24 h-R		Domain-specific PA by PAQ1 (with[b]) versus domain-specific PA by 24 h-R	
	METs	%	r^c	95% CI	r^c	95% CI
24-h Physical activity record						
Sleeping	6.8	16.9	0.51	0.36 to 0.64	–	–
Occupational activity	14.8	36.7	0.31	0.12 to 0.47	0.12	−0.07 to 0.30
Leisure time physical activity	4.6	11.4	0.31	0.13 to 0.47	–	–
Other activity	14.1	35.0	0.09	−0.1 to 0.27	−0.07	−0.26 to 0.12
Total activity	40.3	100.0	0.69	0.57 to 0.77	0.68	0.57 to 0.77

PA Physical activity, *METs* metabolic equivalents, *24 h-R* 24-h physical activity record, *PAQ* physical activity questionnaire, *PAQ1* first survey

[a] Without seasonal variation

[b] With seasonal variation

[c] Spearman's correlation coefficient

during a period of heavy snowfall, and although the subjects worked hard to remove snow, they seldom ventured outdoors. At the time of the second survey, in contrast, they were engaged in planting rice. The second survey in the Saku area was conducted during a cold winter when the subjects may have engaged in less outside farm work. These findings may indicate that physical activity questions should ask about "an average over the year;" otherwise, estimated physical activity depends on the season when the survey was conducted.

In our study, adding the extra working hours of the 'busy season' did not improve the correlation with the 24 h-R estimates, but tended to mitigate the underestimation of total PA calculated with PAQ. Although this can be interpreted as questions about seasonal variation in physical activity not being necessary to estimate average MET-hours over a year, even when such variation exists, the possibility remains that seasonal variation could be more accurately considered using a more sophisticated questionnaire. For example, subjects were asked about the length of the busier season for 1 year and the length of working in the busier season in our questionnaire. This question considered the variability between subjects, but the difference in intensity of working in busier season was not considered.

The limitation of our study was using the 24 h-R as a gold standard. In the 24 h-R, physical activity is calculated using the compendium [16]. In an aging society like in rural Japan, farming or housework may be more labor-saving than previously, and use of the compendium may have overestimated PAs. The higher correlation between PA estimates based on the 24 h-R and PAQ may be attributable to the fact that, because the same conversion table (compendium) was used for physical activity to METs, they had the same direction of measurement error, although the 24 h-R was used as a gold standard in a previous study [13] and its validity to doubly labeled water was confirmed [17].

The PAQ is based on the simple notion that total daily PA consists of four domains, namely occupational activities, including housekeeping and commuting, leisure time activities, sleeping and other activities. This may explain the high validity and reproducibility of this instrument, but may also be the reason for the lack of increase in validity when seasonal variation is considered. Although the domain "occupational activities" includes housekeeping, PA is estimated from hours spent for activities in different levels of intensity, such as sitting, standing, walking and strenuous work, and these categories may not sufficiently represent housekeeping activities. It thus appears possible to improve the PAQ to more precisely determine intensity levels, especially for housekeeping.

In summary, this study shows that our simple PAQ provides a valid estimation of total as well as domain-specific PA in different populations without considering seasonal variation, not only in our JPHC cohort study, but also in broader populations differing by age, sex, residential area, occupation and BMI in epidemiological study.

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Appendix

JPHC Physical Activity Questionnaire

Qa, How many hours do you usually sleep?

( ) hrs

Qb, Do you have 'busier season' than usual during the year?
If you have, please answer the duration of it.

No	less than 1 month	more than 1 month to 2 months	2 to 3 months	3 to 4 months	4-5 months	5-6 months
○	○	○	○	○	○	○
○	○	○	○	○	○	○

Qc, How long did you work on average? Including comuting and household chores.
If you have a 'busier season', please also answer about it.

work hours	less than 1 hr	more than 1hr to 3 hrs	3 to 5 hrs	5 to7 hrs	7 to 9 hrs	9 to 11 hrs	more than 11hrs
1 on average	○	○	○	○	○	○	○
2 in busier season	○	○	○	○	○	○	○

Qd, Please answer the hours spent for each activities about on the average day in the last year.
Including comuting and household chores.

	none	less than 1 hr	more than 1hr to 3 hrs	3 to 5 hrs	5 to7 hrs	7 to 9 hrs	9 to 11 hrs	more than 11hrs
sitting	○	○	○	○	○	○	○	○
standing	○	○	○	○	○	○	○	○
walking	○	○	○	○	○	○	○	○
strenous work	○	○	○	○	○	○	○	○

Qe, Please answer of the leisure time physical activity frequencies and hours spent per one opportunity last year.

exercise	frequency					time spent for one opportunity					
	less than once a month	once to 3 times a month	once to twice a week	3 to 4 times a week	almost every day	less than 30 minutes	30 to 59 mins	1 to 2 hrs	2 to 3 hrs	3 to 4 hrs	more than 4hrs
walking slowly such as taking walk	○	○	○	○	○	○	○	○	○	○	○
walking fast	○	○	○	○	○	○	○	○	○	○	○
light to moderate exercise such as golf, gardening.	○	○	○	○	○	○	○	○	○	○	○
vigorous exercise such as tennis, jogging, aerobics, and swimming	○	○	○	○	○	○	○	○	○	○	○

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Characteristics and Outcomes of Patients With Advanced Gastric Cancer Who Declined to Participate in a Randomized Clinical Chemotherapy Trial

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Abstract

Purpose: There is insufficient data to verify whether participation in clinical trials in itself can lead to better clinical outcomes. We have analyzed the characteristics and outcomes of patients who declined to participate in a randomized trial in comparison with those who participated in the trial.

Patients and Methods: A randomized trial for naive advanced gastric cancer was offered to 286 patients. The trial investigated the superiority of irinotecan plus cisplatin and the noninferiority of S-1 compared with continuous fluorouracil infusion. We retrospectively reviewed the characteristics and outcomes for both participants and nonparticipants in this trial.

Results: Of the 286 patients, 98 (34%) declined to participate in the trial. The rate of declining was significantly higher among younger patients ($P = .003$), and it varied significantly between attending physicians (range, 23% to 58%; $P = .004$). There were no other significant correlations between rate of declining and patient characteristics. No significant differences were observed in the clinical outcomes between the participants and nonparticipants, for whom the median survival times were 367 versus 347 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 1.21 (95% CI, 0.91 to 1.60). No interaction was observed between participation and the various regimens.

Conclusion: There was no difference in clinical outcomes between participants and nonparticipants. However, the patient's age and the doctor-patient relationship may have an effect on patient accrual to randomized trials.

Introduction

A randomized clinical trial (RCT) is the definitive method for comparing the efficacy of treatments, and an RCT is a crucial step in the development of any new cancer treatment. Nevertheless, there is a consistent problem in that low accrual rates limit the progress of RCTs.[1-3]

Several factors that act as barriers to participation in trials have been documented,[1-6] and some have been successfully targeted for improvement.[4-5] Major barriers include a lack of availability of appropriate trials, limitations of eligibility criteria, socioeconomic factors (including insufficient awareness of clinical trials, lack of medical insurance, and geographical limitations), physician triage, and patient decision making. Insufficient data are available on the actual outcomes for nonparticipants in RCTs in comparison with those for participants.[7-11]

We have previously analyzed the characteristics and outcomes of patients who had been referred and were eligible for, but declined to participate in, RCTs and compared them with those of participants, with the aim of developing an approach to improve patient accrual to RCTs.[12] We found no evidence to suggest any significant differences in the characteristics or clinical outcomes between participants and nonparticipants. We also reported that the trial design and the doctor-patient relationship might have an effect on patient accrual to RCTs.

In the present study, we reviewed the characteristics and clinical outcomes of patients who met the eligibility criteria of an RCT designed to compare three different types of therapy, including both injection and oral agents, the levels of toxicity of which were estimated to be quite different. Our analysis was designed to test our previous findings. We also analyzed whether participation in an RCT that compared several arms with different efficacies affected patient outcomes.

Patients and Methods

All the patients who were recruited into this study fulfilled the entry criteria for the Japan Clinical Oncology Group RCT on unresectable or recurrent gastric cancer (JCOG 9912). The patients were informed of all aspects of the trial and were invited to participate. Irrespective of their participation or nonparticipation in the RCT, all received first-line chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between November 2000 and January 2006. Signed informed consent was obtained from the patients to permit future statistical analysis of data from their clinical courses and outcomes, even if they were treated outside the clinical trials.

The RCT was a three-arm, phase III trial conducted by JCOG to investigate the superiority of irinotecan (CPT-11) plus cisplatin (CDDP) combination chemotherapy and the

noninferiority of *S*-1 compared with continuous fluorouracil (FU) infusion.[13]

The criteria for inclusion of patients were as follows: histologically documented unresectable or recurrent gastric cancer; no prior systematic chemotherapy or radiation therapy except for adjuvant chemotherapy with one oral fluoropyrimidine agent other than *S*-1, completed 6 months earlier; age 20 to 75 years; Eastern Cooperative Oncology Group performance status (PS) of 0 to 2; no history of chemotherapy or radiation therapy for malignant disease other than gastric cancer; and adequate hematologic, hepatic, and renal functions. Those with severe peritoneal dissemination resulting in impaired bowel passage, ascites beyond the pelvic cavity, or wall deformity detected by barium enema were excluded. A measurable lesion was not mandatory. Each patient was required to submit written informed consent before taking part in the RCT.

The treatment schedule of each arm was as follows: (1) Continuous FU infusion: FU was infused continuously over 120 hours; this required hospitalization for 7 days. (2) CPT-11 plus CDDP combination chemotherapy: CPT-11 was infused on days 1 and 15, and CDDP was infused on day 1; this required hospitalization for 5 days. (3) *S*-1 monotherapy: *S*-1 was administered orally on days 1 through 28 and repeated every 6 weeks. Patients were required to undergo a medical examination every 2 weeks. Patients who declined to participate ultimately selected their treatment regimen after discussions with their families and physicians. We provided the selected therapies after confirming that patients fully understood that the standard therapy at that time was FU infusion and that the CPT-11 plus CDDP combination therapy and the *S*-1 monotherapy were still under evaluation.

In the RCT, CPT-11 plus CDDP therapy resulted in a longer survival rate, and *S*-1 showed significant noninferiority compared with FU.[13] The hazard ratio (HR) of CPT-11 plus CDDP versus FU was 0.82 (95% CI, 0.68 to 0.99; $P = .019$). The HR of *S*-1 versus FU was 0.83 (95% CI, 0.68 to 1.00, *P* for noninferiority $< .001$). AQ: A

Six male physicians participated in the trial. At the start of the trial (November 2000), physicians A, B, C, D, E, and F had 8, 10, 11, 17, 19, and 19 years of experience, respectively, as gastrointestinal oncologists. One of these six attending staff physicians, together with one, two, or three residents or trainees, attended each consultation. They explained to the patients that this was a JCOG study, that standard therapy was continuous FU infusion, and that we could not tell which arm was superior, but the treatment schedule, toxicities, and required lengths of hospitalization were expected to be different among the various arms. If patients chose not to participate in the study, we recommended the standard therapy, but they could choose other, off-protocol regimens.

We reviewed all the medical records of patients who underwent chemotherapy for unresectable or recurrent gastric cancer between November 2000 and January 2006, and we selected 286 patients who were documented as having been offered the opportunity to participate in the RCT. During the study period, some other patients were judged to be ineligible for the study and were offered other treatments, as clinically indicated, but the number of such patients is not available. Paper and/or electronic medical records from the initial visit to our center to the end of follow-up were reviewed retrospectively. Demographic data (age and sex), medical information (tumor histology, clinical stage, PS, peritoneal dissemination, and therapy characteristics), and clinical outcomes (response rate [RR], follow-up time, overall survival [OS] time, and 1- and 2-year survival rates) were abstracted and analyzed. Response was evaluated by the attending physicians according to the Response Evaluation Criteria in Solid Tumors (RECIST).[14] It is our policy to assess clinical responses to RECIST, even in routine practice. The follow-up time at our institution was defined as the period from the first day of initial therapy to the last visit or the last day of hospitalization at our institution (including death during follow-up). Data on the survival of the patients who left our institution were collected through inquiries to the Japanese official agency for family registries.

The χ^2 test and logistic regression analysis were used to assess associations between patient characteristics and the rate of declining to participate. OS curves were prepared by using the Kaplan-Meier method and were compared with the results of the log-rank test. All participants (those who agreed to be enrolled onto the RCT), including two who were later found to be ineligible after random assignment, and all nonparticipants (those who declined to participate in the RCT), including one who was lost to follow-up, were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (ie, age, sex, histology, clinical stage, PS, nonsevere peritoneal dissemination, and treatment regimen) in comparing the OS of participants and nonparticipants. Interaction between participation and regimen was tested with an α level of 0.2; $P < .05$ was regarded as significant. Collected data were analyzed by using an SPSS II statistical package (SPSS, Chicago, IL). This study was approved by the institutional review board at the National Cancer Center and was conducted in accordance with the ethical principles stated in Japanese ethics guidelines for clinical and epidemiological studies. No patient explicitly refused to be analyzed for his or her outcome during this study period. The institutional review board approved the use of such clinical data for the study objective.

Results

Table 1 shows the patient characteristics and the rates of declining. A total of 190 patients accepted, and 96 patients (34%) declined, entry into the RCT. There was no significant correlation between the declining rate and sex, clinical stage, PS, tumor histology, or peritoneal dissemination. Patients younger than 60 years declined to participate at a significantly higher frequency ($P = .003$). There were also significant differences in the declining rates between the various attending physicians who informed the patients about the trial and asked for their participation ($P = .004$). The patients were divided equally among the offering physicians by characteristic. T1

Table 1. Patient Characteristics and Rate of Declining to Participate in Randomized Clinical Trials

Characteristic	Participants		Non-participants			Participants			Nonparticipants		
	No.	%	No.	%	ROD (%)	OR	95% CI	P	OR	95% CI	P
No.	190		96		16						
Sex											
Male	146	77	64	67	30	1.66	0.97 to 2.85	.07	0.49	0.26 to 0.90	.02
Female	44	23	32	33	42						
Age, years											
< 60	48	25	41	43	46	0.45	0.27 to 0.76	.003	2.54	1.44 to 4.47	.01
≥ 60	142	75	55	57	28						
Clinical stage											
III	1	1	0	0	0						
IV	146	77	70	73	32	1.30	0.74 to 2.26	.36	0.55	0.29 to 1.04	.06
Recurrent	43	23	26	27	38						
PS											
0	104	55	51	53	30						
1	84	44	44	46	34	0.96	0.58 to 1.58	.87	0.85	0.49 to 1.47	.56
2	2	1	1	1	33	0.98	0.09 to 11.07	.99	0.51	0.03 to 7.04	.61
Histology											
Well differentiated	75	39	34	35	31	0.85	0.51 to 1.42	.55	1.05	0.59 to 1.89	.86
Poorly differentiated	115	61	61	64	35						
Undifferentiated	0	0	1	1	100						
Peritoneal dissemination											
Yes	85	45	51	53	38	0.71	0.44 to 1.17	.18	1.54	0.89 to 2.69	.13
No	105	55	45	47	30						
Physicians											
A	31	16	19	20	38			.04			< .01
B	27	14	10	10	27						
C	35	18	13	14	27						
D	25	13	27	28	52						
E	67	35	20	21	23						
F	5	3	7	7	58						

NOTE. Univariate analysis was performed with Pearson's χ^2 test; multivariate analysis was logistic regression analysis.
Abbreviations: ROD, rate of declining; OR, odds ratio; PS, performance status.

T2 Table 2 shows the treatment options of patients who declined to participate in the RCT. Nearly 60% of all those who declined to participate selected *S*-1 monotherapy. Moreover, approximately 70% of nonparticipants who were under 60 years of age selected *S*-1 monotherapy. The proportion of those who selected CPT-11 plus CDDP, which was expected to be more beneficial but showed more severe toxicity and required hospitalization, was not necessarily higher among nonparticipants younger than 60 years than among older nonparticipants. No specific tendency was shown in selection of regimen in relation to the attending physician.

AQ: B Post-therapy was analyzed in 188 of the participants. This group excluded all 96 nonparticipants, as well as two patients found to be ineligible after random assignment: one patient who developed gastrointestinal bleeding several hours after entry, and another who was later diagnosed with adenosquamous cell carcinoma. Survival was analyzed in the 190 participants and the 96 nonparticipants. There were no treatment-related deaths among either the participants or the nonparticipants. There was no difference in the number of cycles of first-line chemotherapy received by participants or nonparticipants: 53% of the participants and 58% of the nonparticipants received fewer than three cycles ($P = .406$). A total of 85% of the participants and 70% of the nonparticipants were given more than two chemotherapy regimens. Statistically, more participants than nonparticipants were given chemotherapy after the initial therapy ($P = .003$). A total of 14 (7%) of the participants and 6 (6%) of the nonparticipants in the RCT participated later in early-phase clinical trials of experimental therapies.

There were no major differences in clinical outcome between participants and nonparticipants (Figure 1). Clinical response to F1,AQ:C the initial therapy was analyzed in all 190 participants and 96 nonparticipants. The RR was 30.5% for the participants and 21.9% for the nonparticipants ($P = .121$). The median follow-up time at our hospital was not significantly different between the participants (317 days) and the nonparticipants (292 days). The median survival time (MST) was 367 days for the participants and

Table 2. Characteristics and First Treatment Regimen of Nonparticipants

Characteristic	FU		CPT-11 Plus CDDP		S-1		P*
	No.	%	No.	%	No.	%	
No.	31		8		57		
Sex							
Male	22	34	5	8	37	58	.819
Female	9	28	3	9	20	63	
Age, years							
< 60	10	24	3	7	28	68	.297
≥ 60	21	38	5	9	29	53	
Clinical stage							
IV	20	29	6	9	44	63	.438
Recurrent	11	42	2	8	13	50	
PS							
0	15	29	6	12	30	59	.641
1	16	36	2	5	26	59	
2	0	0	0	0	1	100	
Histology							
Well differentiated	10	29	4	12	20	59	.814
Poorly differentiated	21	34	4	7	36	59	
Undifferentiated	0	0	0	0	1	100	
Peritoneal dissemination							
Yes	16	31	1	2	34	67	.043
No	15	33	7	16	23	52	
Physicians							
A	5	26	1	5	13	68	.363
B	4	40	3	30	3	30	
C	4	31	0	0	9	69	
D	8	30	2	7	17	63	
E	8	40	2	10	10	50	
F	2	29	0	0	5	71	

Abbreviations: FU, fluorouracil; CPT-11, irinotecan; CDDP, cisplatin; PS, performance status.
* Pearson's χ^2 test.

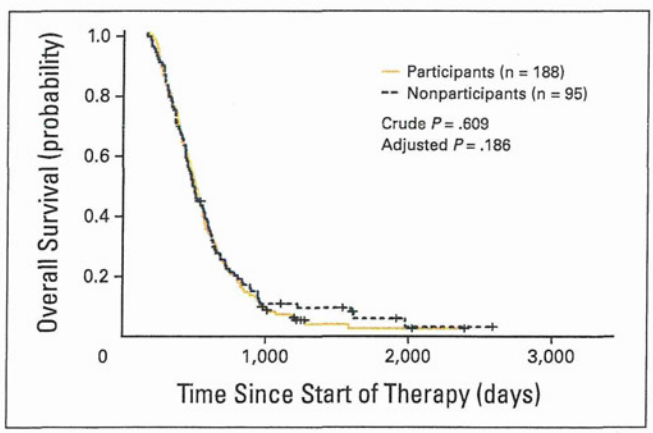

Figure 1. Overall survival of nonparticipants in randomized trials compared with that of participants. No significant difference were observed.

347 days for the nonparticipants. There were no significant difference in OS between the participants and the nonparticipants (Figure 1), and the HR was 1.07 (participants *v* nonparticipants; 95% CI, 0.83 to 1.38). With the Cox proportional hazards model adjusted for sex, age, tumor histology, clinical stage, PS, peritoneal dissemination, and treatment regimen, the HR of participants versus nonparticipants was 1.21 (95% CI, 0.91 to 1.60; $P = .19$). Furthermore, the RR and OS were not significantly different between the participants and the nonparticipants for each regimen. The RR in participants versus nonparticipants was 9.5% versus 6.5% for FU ($P = .646$), 54.0% versus 62.5% for CPT-11 plus CDDP ($P = .648$), and 28.1% versus 24.6% for *S*-1 ($P = .657$). MST in participants versus nonparticipants was 358 days versus 335 days for FU, 435 days versus 458 days for CPT-11 plus CDDP, and 338 days versus 345 days for *S*-1. The HR values for OS were 0.91 (95% CI, 0.57 to 1.44; $P = .679$) for FU, 0.99 (95% CI, 0.38 to 2.56; $P = .981$) for CPT-11 plus CDDP, and 1.22 (95% CI, 0.81 to 1.83; $P = .333$) for *S*-1 (Appendix Figures A1-A3, online only).

We analyzed the interaction between participation and regimen. The *P* value for the interaction term was greater than the α level of 0.2; it was 0.75 for participants and CPT-11 plus CDDP, and 0.28 for participants and *S*-1 (Appendix Table A1, online only).

Discussion

We previously analyzed the characteristics and outcomes of patients who had been referred and were eligible for, but declined to participate in, two RCTs for naive, advanced, non–small-cell lung cancer and compared them with those of participants.[12] Trial 1 was a comparison of four similar combinations of injection therapies (cisplatin-irinotecan, carboplatin-paclitaxel, cisplatin-gemcitabine and cisplatin-vinorelbine), and Trial 2 compared two sequences of injection and oral therapies (four courses of carboplatin-paclitaxel followed by gefitinib or gefitinib until disease progression, followed by carboplatin-paclitaxel). We found that the rate of declining to participate in a trial in which similar injection therapies were compared was lower than that in a trial in which injection and oral therapies were compared (16% *v* 37%). We also reported that there was no evidence to suggest any difference, except for that of the attending physician, in the characteristics and clinical outcomes between participants and nonparticipants.

In the present study, we compared three different regimens, two of which were given by injection and the other as an oral agent. The rate of declining in the present study was 34%, which was as high as that of Trial 2 in our previous study. It is easy to understand that more difficulty is experienced in accepting the randomization of different types of therapy.[8,15] The therapy arms of the present study used different methods of administration; moreover, the estimated toxicities and the need for hospitalization were quite different among the various arms. We thus confirmed our previous finding that trial design influences trial accrual.

Nearly 60% of those who declined entry into the trial selected *S*-1 monotherapy, which may reflect the patients' desire for convenience and a higher quality of life. Younger patients, in particular, preferred this oral agent. We speculate that they may attach greater importance to avoiding hospitalization than to uncertain efficacy. This difference between age groups was a new finding of the present study.

As noted in our previous report, the rate of declining also appeared to be greatly affected by the attending physician. No record was available of which person actually took the initiative and offered the trial at each consultation; however, even when a resident or trainee offered the trial, the attending physician would have taken the responsibility for the consultation. No relationship was found between the length of experience of the physician as a gastrointestinal oncologist and the rate of declining. Each attending physician attempted to present the three regimens equally without showing favor toward any particular regimen; this suggests that individual consultations were not the source of bias. Physicians' clinical communications have been noted as affecting patients' decision making regarding participation in clinical trials.[16] Improved communications and more frequent interventions by clinical research coordinators and other medical staff members for all eligible patients might improve the accrual rate.[17-19] This study did not clarify whether differences in communication skills between physicians led to differences in rates of declining; further investigations of this effect are warranted.

On the other hand, inadequate data are available on the actual outcomes for RCT nonparticipants compared with those of participants.[7-11] Although several reports and a review[7] have suggested the existence of a "trial effect" in which participants enjoy more favorable outcomes, other studies, especially those that attempted to exclude confounding factors, have refuted this finding.[8-11] Our study revealed that the outcomes for participants were no better than those of nonparticipants. Furthermore, our results showing that interactions between participants or nonparticipants and the treatment regimen were not significant (Table 3) may suggest that the conclusion of this RCT could be generalized. The HR for OS between participants and nonparticipants was very close to 1 (0.91; 95% CI, 0.57 to 1.44) in the FU arm, which was the control arm in the trial, and numerically favorable for nonparticipants in the CPT-11 plus CDDP arm and the *S*-1 arm (CPT-11/CDDP: 0.99; 95% CI, 0.38 to 2.56; *S*-1: 1.22; 95% CI, 0.81 to 1.83), which were the testing arms in the trial. This suggests the possibility of a self-selection bias.

Our study has several limitations. First, we selected the participants and nonparticipants retrospectively among those who underwent chemotherapy for advanced gastric cancer during the period in which we conducted the RCT. The fact that all the patients accepted treatment of some sort is, in itself, a selection process, and information on patients who declined all active treatments at our institution remains elusive. There may have been some patients who did not want to continue active treatment and who instead opted for supportive care only, or other patients who declined to participate in the RCT and went to other hospitals. We did not review this population, and if there were any such patients, this may have affected the survival analysis.

Second, the present study was conducted at a single academic institution, and there was an insufficient number of patients. As a result, the numbers of patients in the various subsets were quite small, and it is difficult to rule out significant differences in some of these because of a lack of statistical power. Our investigation should therefore be interpreted as exploratory and hypothesis generating. Our results require further validation at other institutions, preferably on a multi-institutional basis, because the situation may well be different at other institutions.

Third, no data were available regarding the reasons for participation or nonparticipation. Such information would be useful for analyzing factors that affect consent or refusal to participate and would help in improving the accrual rate. However, so that patients are not coerced into participating in the study, reasons for their participation or refusal need to be collected by independent investigators.

In conclusion, we confirmed that the rate of declining to participate in RCTs was influenced by the design of the trial and by the referring physician. The age of the patients also had an effect on the rate of declining, suggesting that some patients may attach a greater importance to not having their normal schedule disrupted than to expectations of efficacy. There was no evidence of any difference in the RRs and survival times between participants and nonparticipants, and the interaction between participants or nonparticipants and the treatment regimen was not significant.

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AQ: D ***Authors' Disclosures of Potential Conflicts of Interest***

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

TA1, FA1-FA3

Table A1. Interaction Between Participation and Treatment Regimen

Variable	HR*	95% CI	*P*
Participant *v* nonparticipant†	1.01	0.65 to 1.57	.96
CPT-11 + CDDP *v* FU	0.42	0.17 to 1.02	.06
S-1 *v* FU	0.54	0.34 to 0.86	.01
Participant and CPT-11 + CDDP	1.19	0.45 to 3.16	.72
Participant and *S*-1	1.37	0.77 to 2.44	.29

Abbreviations: HR, hazard ratio; FU, fluorouracil; CPT-11, irinotecan; CDDP, cisplatin; FU, fluorouracil.
* HRs and 95% CIs were obtained by using a Cox proportional hazards model adjusted for sex, age, histology, clinical stage, performance status, and peritoneal dissemination.
† Right-hand sides were used as the reference groups.

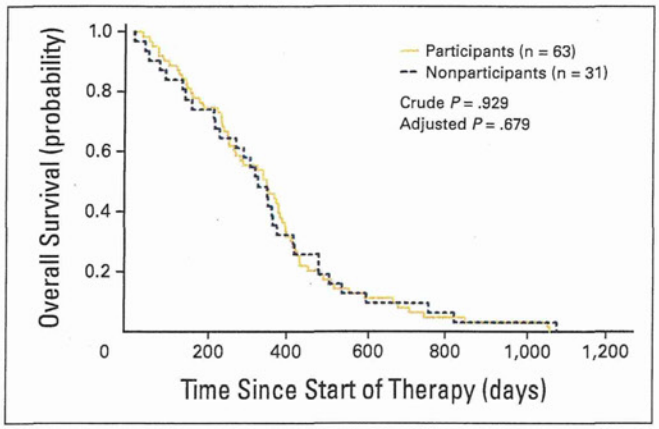

Figure A1. Overall survival of patients who were treated with fluorouracil.

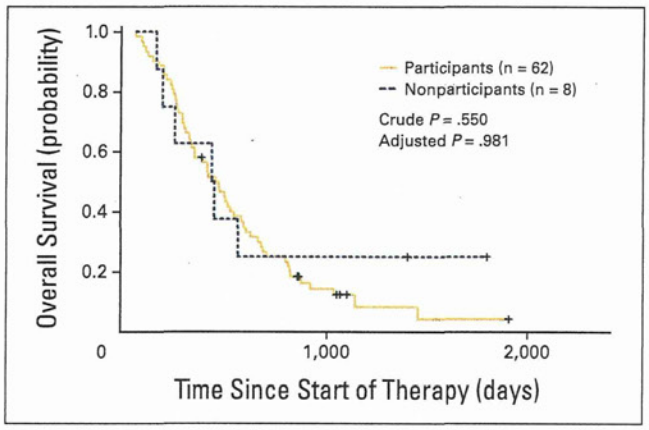

Figure A2. Overall survival of patients who were treated with irinotecan plus cisplatin.

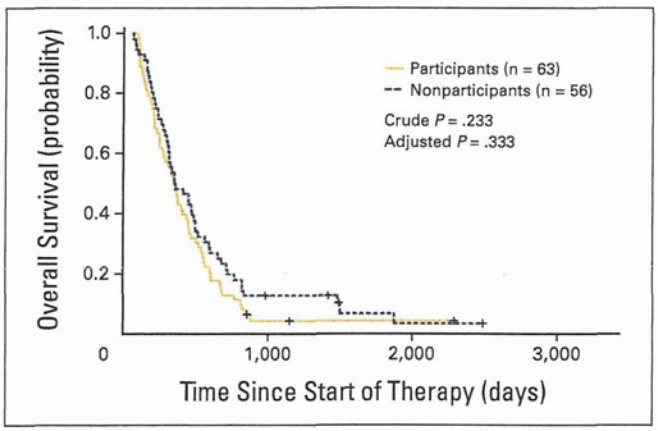

Figure A3. Overall survival of patients who were treated with *S*-1.

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Review Article

Risk factors for breast cancer: epidemiological evidence from Japanese studies

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Although our understanding of the etiology of breast cancer has improved, many well-known risk factors are not modifiable and present knowledge has proved insufficient to allow the disease to be overcome. Indeed, incidence and mortality among Japanese women have increased over the past three decades. Here, we review epidemiological evidence from our cohort and case–control studies among Japanese women in comparison with other published findings. Our studies confirm the important role of established factors derived primarily from Western populations, such as menstrual and reproductive factors, anthropometric factors, physical activity, and alcohol intake, in the development of breast cancer. In addition, we provide further evidence to better understand the role of traditional Japanese foods in the etiology of breast cancer. Our cohort study found that a higher intake of isoflavone and higher levels of plasma genistein, but not daidzein, were associated with a decreased risk of breast cancer. Our case–control studies reveal a dose–response pattern for these compounds; specifically, decreased risk as women move from "no" to "moderate" intake and leveling off thereafter. In addition, gene–environment interactions have been revealed in the effects of isoflavones. The evidence reviewed suggests that isoflavone has a protective effect against breast cancer in Asian populations. Conversely, our cohort study did not observe an inverse association between breast cancer risk and the intake of green tea and/or the plasma level of tea polyphenols, but we did find an association between increased risk and active and passive smoking. In conclusion, based on current knowledge, primary prevention according to individual lifestyle modification should focus on alcohol intake, weight control, physical activity, and tobacco smoking. (*Cancer Sci* 2011; 102: 1607–1614)

The incidence and mortality rates of breast cancer vary considerably across countries and regions, with a four to five-fold variation in incidence. Rates are highest in Europe and North America and lowest in Asia.[1] Despite Japan's status as a low-risk country, the incidence and mortality of breast cancer among Japanese women have increased over the past three decades (Fig. 1),[2–5] with age-standardized incidence rates (per 100 000 population) of 17.0 in 1975 compared with 44.4 in 2005 according to the Monitoring of Cancer Incidence in Japan (MCIJ) project.[6] Breast cancer is the most common cancer diagnosis and the fourth-leading cause of cancer death among Japanese women. For example, in 2005 the MCIJ estimated that more than 47 583 Japanese women were diagnosed with breast cancer[6] and that 10 721 died of it.[7] In contrast, mortality rates in the UK and US have been in decline since the early 1990s, possibly attributable to improvements in screening practices and treatment effectiveness.[3,8] Moreover, incidence rates in the US and several other developed countries have decreased since 2002, due, in part, to the results of the Women's Health Initiative's randomized trial in July 2002, which saw a rapid fall in the use of hormone-replacement therapy (HRT).[9]

In addition to differences in the incidence and mortality rates of breast cancer between Asian and Western countries, age-specific incidence curves also differ: in Japan, the incidence of breast cancer increases until 50 years of age and decreases or plateaus thereafter, whereas in Western countries the incidence of breast cancer continues to increase after 50 years of age (Fig. 2).[2] This pattern may be explained by differences in the distribution of risk factors for postmenopausal breast cancer, particularly the low prevalence of obesity and HRT use in Japan.[10,11] Of note, the rapid rise in rate with increasing age slows somewhat around 50 years of age, near the time of menopause, which strongly suggests a role for reproductive hormones in the etiology of this disease.

Geographical distribution and secular trends in cancer incidence and mortality, as well as studies of migrants, highlight the relative importance of environmental and lifestyle influences in cancer etiology. Studies in migrants have shown increases in breast cancer incidence and mortality following migration from a lower- to a higher-risk country.[12–14] For example, Japanese immigrants in Los Angeles County had a clearly higher rate of breast cancer than Japanese in Japan.[12] Furthermore, the incidence of breast cancer in first-generation Japanese immigrants in São Paulo from 1968 to 1978 was higher than that among Japanese living in Japan, whereas mortality increased from 1979 to 2001 to a rate intermediate between that of Japanese living in Japan and Brazilians living in the state of São Paulo.[13,14] These findings strongly suggest that breast cancer risk is influenced by factors associated with the lifestyle or environment of the destination country.

Current knowledge of preventive or risk factors

Accumulating evidence obtained mainly from Western countries has established a relatively large number of preventative or risk factors for breast cancer (Table 1).[15–17] Many established risk factors are linked to ovarian hormones, and estrogens in particular, and prospective studies in postmenopausal women have shown a direct association between higher levels of estrogens and their androgen precursors and an increased risk of breast cancer.[18] One possible biological mechanism of the effect of ovarian hormones on risk is that both endogenous and exogenous hormones increase cellular proliferation in the breast, thereby increasing the likelihood of random genetic errors during cell division.[19]

Although our understanding of the etiology of breast cancer has improved, many well-known risk factors, such as menstrual

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