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Clinical Topics in Japan

Fundamental Problems with Clinical Guidelines Developed in Japan

Tsuguya Fukui*1

Following Canada, the United States, and European countries, clinical guidelines have become ubiquitous in Japan both inside and outside the medical community. Clinical guidelines for the use of CT scanning[1] and gastric cancer[2] cited in this issue of *the Journal* reflect this.

Clinical guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" as defined by Institute of Medicine in 1990.[3] Reference to "patient decisions" in this definition undoubtedly results from the notion of patient-centered medicine; a paradigm that has influenced clinical practice since the late 20th century. The remaining part of the definition, concerning the development of "statements to assist practitioners," is a practice likely to have been in existence since the outset of the history of medicine thousands of years ago. As Steven H. Woolf describes, there are at least four methods of developing clinical guidelines; informal consensus development, formal consensus development, evidence-based guideline development, and explicit guideline development.[4] Of these, the method required for current clinical guidelines is evidence-based development.

In 1999 when the Ministry of Health, Labor and Welfare of Japan decided to invest research grants into an evidence-based development program for clinical guidelines. A variety of groups of physicians, mainly from specialist societies concerned with diseases targeted by a government committee according to disease burden, have started to formulate clinical guidelines. To date at least 23 clinical guidelines have been developed in this framework. Many more, possibly hundreds of clinical guidelines, have been developed outside this framework. There is a high expectation that the quality of medical care can be ensured by the use of clinical guidelines and that this may also resulting in better patient outcomes as indicated[5] in the previous issue of *the Journal*.

There are, however, several problems which have come into focus during the course of clinical guideline development. Some appear easy to solve and others more difficult to solve in a short time. For example, some clinical guidelines have not been formulated according to evidence-based methodology in its true sense. Further, there are wide variations in the format of guideline presentation. As a result, users have difficulty in finding appropriate recommendations and the evidence to support them. In this regard, I have been advocating a clinical question driven style, such that each set of guidelines begin with the statement of a clinical question, and followed immediately by an answer, formalized as recommendations that are graded according to the classification adopted by the guideline development committee, and accompanied by a reason for those recommendations in the form of evidence classified by level also according to the committee. A brief explanation and a list of references would then follow the recommendations and evidence.

The most serious among the problems concerns the scarcity of high quality evidence originating from Japan. In fact I often heard leaders engaged in the development of clinical guidelines lamenting over the lack of high quality research articles originating from Japan and thus frequently having difficulty determining the degree to which the recommendations are supported by research, i.e., the issue of the external validity of the evidence they cited. Mahbubur Rahman and I have pointed out the weakness of Japanese academic activity in clinical research based on our findings of the truly meager contribution of articles from Japan to highly reputed clinical journals in contrast to Japan's tremendous contribution in terms of total publications of articles and relatively high contribution to basic research in the global profile.[6,7] Furthermore Rahman et al. show in this issue of *the Journal* that study designs yielding high quality evidence to support recommendations were relatively rarely adopted by clinical researchers in Japan.[8]

Japanese medicine's weakness in clinical research has its origin in the system of medical education adopted at the University of Tokyo about 130 years ago during the Meiji era. Medicine in Japan has since been dominated by German-style biomedicine resulting in an academic atmosphere that does not adequately appreciate the potential contribution of epidemiological studies. In fact not one single school of public health existed until 5 years ago when Kyoto University established the first in Japan. And thus there has been no way of guiding physician researchers to the field of clinical epidemiology, an academic discipline which is a sine qua non of conducting high quality clinical research.

Of course recognizing Japan's weakness in clinical research activities is the first step towards augmenting Japan's contribution to clinical medicine in the future. Clinical guidelines full of recommendations supported by high quality of evidence originating from Japan will be developed only with the growth and diffusion of the discipline of clinical epidemiology as a basic science for all clinical practitioners in Japan.

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*1 St. Luke's International Hospital, Tokyo
Correspondence to: Tsuguya Fukui MD, MPH, PhD, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan.
Tel: 81-3-3541-5151, Fax: 81-3-3544-0774, E-mail: fkts@luke.or.jp

Study Designs Used by Japanese Clinical Researchers: A quantitative estimate of randomized controlled trials, cohort studies, case-control studies and meta-analysis

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Mahbubur Rahman,*1 Mayuko Saito,*2 Tsuguya Fukui*2

Abstract

Background Japanese biomedical researchers are said to have been using less sophisticated study designs in terms of clinical research, and studies on quantitative estimates based on randomized controlled trials (RCT), cohort studies (CS), case-control studies (CCS) and meta-analyses (MA) are not available in this regard to date.

Methods We searched PubMed database to estimate the number of RCT, CS, CCS and MA published by Japanese researchers during the period 1994–2003, and compared it with that of rest of the countries as a whole. The search criteria we employed included publication year (1994–2003), language (English), tag (human), publication type (MA, RCT), and medical subjects headings (cohort studies, case-control studies, odds ratio). Nonparametric tests for trends were performed to determine any significant changes in the number and proportion of publication types over the period in question.

Results During the period 1994–2003, 98,774 RCT, 174,898 CS, 5,489 CCS, and 6,993 MA were published as a whole while Japanese researchers contributed 3,148 (3.19%), 8,985 (5.36%), 268 (4.03%), and 62 (0.89%) papers respectively. For the year 1994, the respective percentages were 2.58%, 4.02%, 2.25%, and 0%, and for the year 2003 they were 3.39%, 5.36%, 5.49%, and 1.15%. Japan's contribution has increased significantly over the period of time, in all categories in absolute terms, but not always in proportion to the total number of articles in respective categories.

Conclusions Although the number of publications has increased over time, the Japanese share of published studies in RCT, CS, CCS and MA categories were lower compared with the average figures for the rest of the world.

Key words Randomized controlled trials, Meta-analysis, Cohort studies, Case-control studies, Japan, Research productivity, Biomedical publication, Research design

Introduction

Randomized controlled trials (RCT), cohort studies (CS), case-control studies (CCS) and meta-analysis (MA) are considered to be very important study designs in terms of generating evidence for clinical practice.[1] However, it has been reported that Japanese clinical researchers have not been using the more sophisticated study designs to help accumulate clinical evidence.[2] Different studies have shown that Japan contributed 8.8% of the total journal articles indexed in Pubmed,[3] 1.1% of epidemiology

*1 Marshfield Epidemiology Research Center, Marshfield, USA
*2 Clinical Practice Evaluation and Research Center, St. Luke's Life Science Institute, St. Luke's International Hospital, Tokyo
Correspondence to: Mahbubur Rahman MBBS, MPA, PhD, Marshfield Epidemiology Research Center, 1000 North Oak Avenue, Marshfield, WI 54449, USA. Tel: 1-715-389-3509, Fax: 1-715-389-3880, E-mail: rahmanmdm@yahoo.co.uk

Table 1 Summaries of search strategy and criteria used to identify articles with different study designs based on Medline database

Randomized Controlled Trials (RCT)
randomized controlled trial [ptyp] AND ("1994" [PDAT]: "2003" [PDAT]) AND (Japan [affiliation] OR Tokyo [affiliation] OR*) AND English [Lang] AND "Human" [MeSH] NOT (Editorial [ptyp] OR Letter [ptyp] OR Practice Guideline [ptyp] OR meta-analysis [ptyp] OR Review [ptyp])

Cohort Studies (CS)
"Cohort Studies" [MeSH] AND ("1994" [PDAT]: "2003" [PDAT]) AND (Japan [affiliation] OR Tokyo [affiliation] OR*) AND English [Lang] AND "Human" [MeSH] NOT (randomized controlled trial [ptyp] OR Editorial [ptyp] OR Letter [ptyp] OR Practice Guideline [ptyp] OR meta-analysis [ptyp] OR Review [ptyp])

Case-control Studies (CCS)
"Case-control studies" [MeSH] AND "odds ratio" [MeSH] AND ("1994" [PDAT]: "2003" [PDAT]) AND (Japan [affiliation] OR Tokyo [affiliation] OR*) AND English [Lang] AND "Human" [MeSH] NOT (randomized controlled trial [ptyp] OR Editorial [ptyp] OR Letter [ptyp] OR Practice Guideline [ptyp] OR meta-analysis [ptyp] OR Review[ptyp])

Meta-analysis (MA)
Meta-analysis [ptyp] AND ("1994" [PDAT]: "2003" [PDAT]) AND (Japan [affiliation] OR Tokyo [affiliation] OR*) AND English [Lang] AND "Human" [MeSH] NOT (Editorial [ptyp] OR Letter [ptyp])

* All possible Japanese cities, prefectures and University names have been included to avoid the possibility of exclusion of articles from Japan, due to some articles being without country or city affiliation.

articles,[4] 0.6–11.4% of clinical science articles [5–18] and 3.8–11.9%[19] of articles in basic science categories. However, no estimate is available for the Japanese contribution to the range of different study design categories, although one study has reported on RCT based on 1995–1999 data.[20] The objective of the present investigation was to quantify RCT, CS, CCS and MA that originated from Japan and to compare this with that of other countries as a whole.

Methods

We searched PubMed in February 2005 to obtain the total number of RCT, CS, CCS and MA indexed in this database and published during the period 1994–2003. Subsequently, a similar search was performed to generate the number of publications by authors affiliated to Japanese institutions. To identify the percentage of the Japanese contribution to a particular study design category, we used the number of articles with the study design affiliated to Japanese institutions as numerator, while the total number of articles with similar design originated from all over the world was used as denominator. In addition, we conducted a search on the total number of journal articles (excluding published letters) that originated from Japan and the rest of the world together to elicit the proportion of a particular study design article relative to the total number of articles.

We used another indicator based on the total number of a particular study design affiliated to Japanese institutions as numerator and total articles from Japan in all categories as denominator. The search strategies and criteria used to find the relevant information are listed in Table 1. We used 'publication type' option for RCT and MA, and Medical Subject Headings (MeSH) words for CS ("cohort studies") and CCS ("case-control studies" and "odds ratio") as other options were not available to identify the numbers in the latter two categories. Separate estimates for each year (from 1994 to 2003) were generated with a view to examining the trend over the whole period of time.

Statistical Analysis

Trends for the total number and proportion of articles with different study design that originated from Japan and the rest of the world were examined using non-parametric tests for trends.

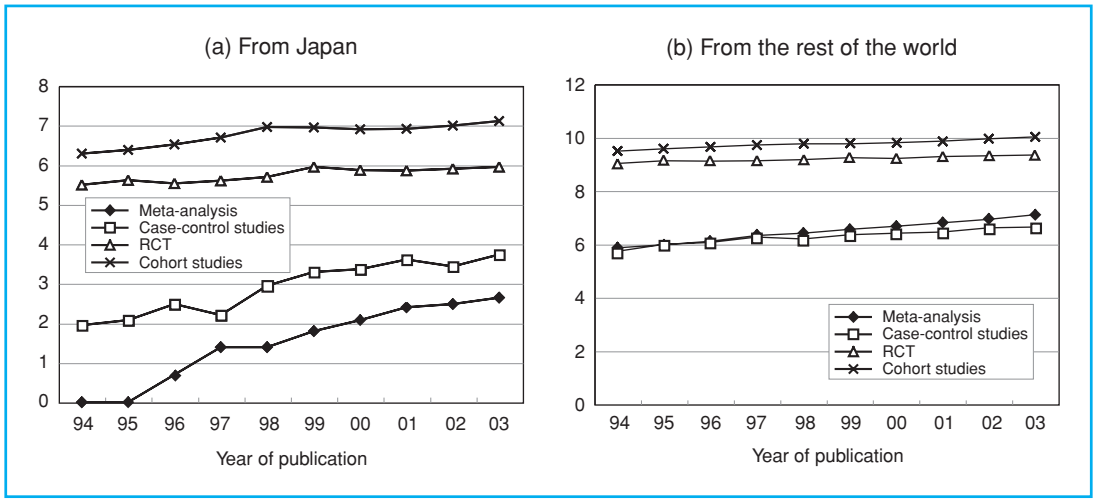

Fig. 1 Number of articles in the Pubmed database during 1994–2003 based on different study designs in logarithm scale: (a) from Japan and (b) from the rest of the world

Y-axis indicates the number of publications in logarithm scale. The numbers have increased significantly over the period of time in all categories as P values were always less than .05 for each of the categories both for articles from Japan and the rest of the world in logarithm and normal scale.

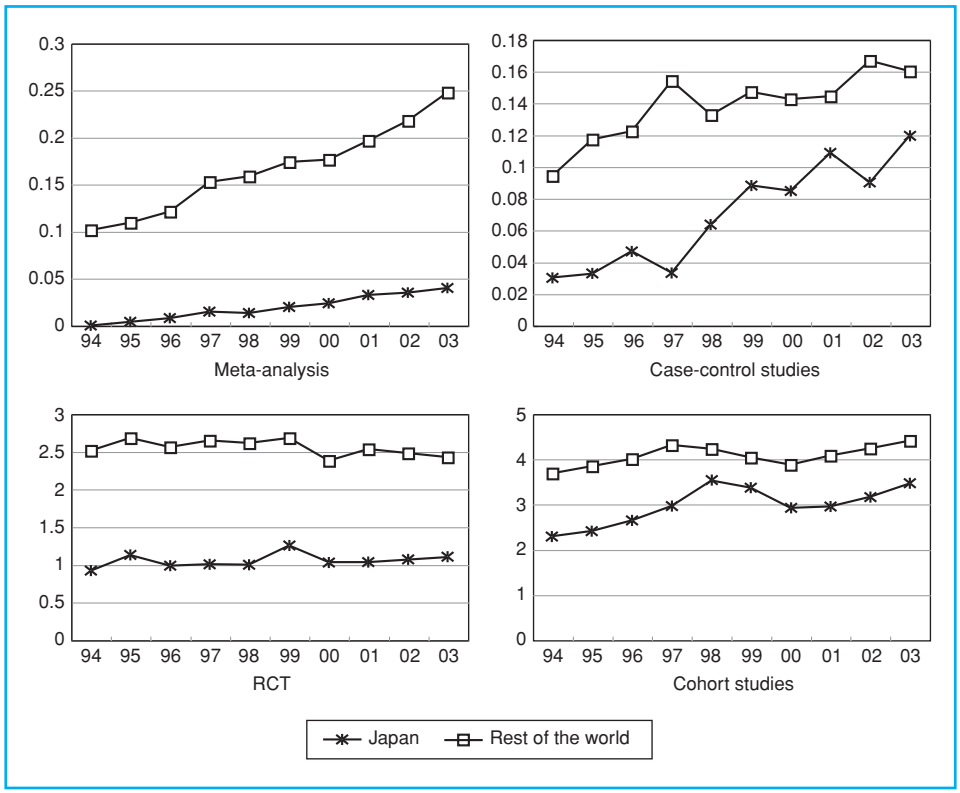

Fig. 2 Comparison of Japanese contribution in each of the research study design categories with that of the rest of the world

X-axis indicates year of publication while y-axis indicates percentage of total articles in respective categories. In CS, CCS and MA categories, Japan and the rest of the world's contribution as a proportion of the total articles were found to have increased significantly. In RCT however, the contributions remained unchanged.

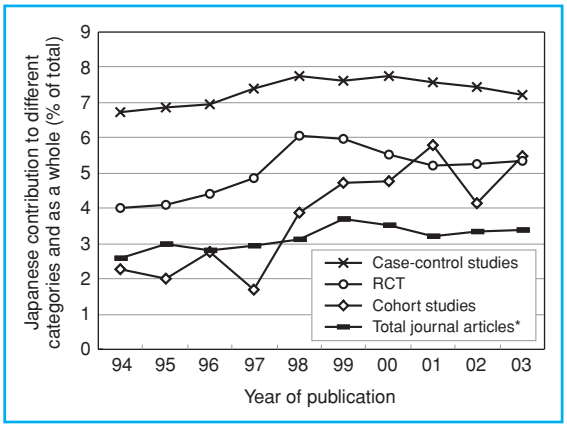

Fig. 3 Japan's share of articles in different categories of study design, and as a whole (based on Pubmed database)

Numerators were the number of articles from Japan in each category of study design, while the denominators were total number of articles in Pubmed database in that category.

* In this case the numerator was total number of articles from Japan (excluding published letters) and the denominator was total number of articles indexed in Pubmed database.

All analyses were performed using Stata statistical software 7 (Intercooled).[21]

Results

Overall numbers

From 1994 up to December 2003, 98,774 RCT, 174,898 CS, 5,489 CCS, and 6,993 MA were published as a whole while Japanese researchers contributed 3,148 (3.19%), 8,985 (5.36%), 268 (4.03%), and 62 (0.89%) articles, respectively. The respective figures were 2.58%, 4.02%, 2.25%, and 0% during 1994, and 3.39%, 5.36%, 5.49%, and 1.15% during 2003. In terms of number, both Japanese and the rest of the world's contributions have increased significantly over time in each of the categories. Figure 1 shows contribution trends from Japan and the rest of the world in logarithm scale.

Contribution as a share of total articles indexed in pubmed

Figure 2 presents articles from Japan and the rest of the world in each of the RCT, CS, CCS, and MA categories as a proportion of total articles from the respective category as indexed in the Pubmed database. Both Japanese and the rest of the world's share of published articles have increased significantly in CS (P = .05 vs .04), CCS (P = .01 vs .01), and MA (P = .01 vs .01) categories over time and remained unchanged in RCT category (P = .16 vs .13).

Japanese situation as a proportion of total articles in a particular study design

Figure 3 shows the Japanese position in terms of proportion of total articles in a particular study design category. Japan's share as a proportion of total articles has increased in RCT (P = .02), CCS (P = .01) and MA (P = .01) categories significantly and marginally in CS (P = .08) categories. On the other hand, the Japanese overall share of articles has remained unchanged during this period (P = .12).

Discussion

This study presents information on Japan's contribution to each of the categories of study design, which helps generate evidence for clinical practice. In terms of number, Japan's contribution has increased over the period in question, but not always proportionally. Japan's contribution to different categories of study design articles are comparable to that of high impact factor journals in different subject areas.[3–19] Its share of RCT was a little lower if we compare it to that reported for the publication period 1995–1999 (5% of total).[20] This could be due to the fact that more stringent inclusion criteria were set up in this study (reviews, letters, practice guidelines and editorials were all excluded). Japan's contribution to MA design was generally lower, but comparable in the case of highly reputable general medicine (0.7% of the total)[18] and epidemiology journals (1.1% of total).[4] Journals in the general medicine and epidemiology categories use epidemiological study designs which are not wide-spread among clinicians and researchers in Japan. MA is one of the latest epidemiological study designs, which summarizes a group of studies/trials to provide pooled evidence. Thus it is not surprising that Japanese contribution to MAs articles (0.89%) was far lower than its overall contribution to biomedical articles (8.8%).[3]

There are limitations to this study. Since there are no options available in Pubmed database to quantify the number of case-control and cohort studies, we estimated the numbers based on MeSH words which might not represent the

actual number in this regard. Again, we included articles indexed in PubMed database only, while there could be additional articles in other databases, and some articles from Japan and other countries could remain unpublished or simply as reports. In this case, our estimates could differ somewhat if the proportions from Japan and other countries were different in this regard.

Although the average Japanese contribution (as a proportion of total articles originated from Japan) to a particular study design was lower compared to that of the rest of the world (as a proportion of total articles from the rest of the world), the situation has improved significantly over the last 10 years. Policy makers and clinical researchers need to work together to improve this situation further. The language barrier, funding shortages for clinical research and the lack of appropriate infrastructure are the main areas that require initial attention. A few other steps are also necessary for a visible improvement to be achieved in the near future. First, in order to improve the situation, it is crucial that the undergraduate and graduate students currently enrolled in clinical and public health departments be made aware of methodologies related to RCT, CS, CCS and MA. Second, to facilitate clinical research with sophisticated study designs, faculty experienced in clinical/epidemiological research should be recruited. Third, there should be training programs on how to write scientific articles in English for the clinical researchers in Japan. These programs should be conducted by noted scholars from the English speaking countries.

In conclusion, the number of articles with sophisticated study designs that originated from Japan is not up to the mark if we compare it with the average from the rest of the world, although it has increased over the period of time analyzed. Appropriate interventions are a prerequisite to improving the situation.

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Original Article

Prevalence of Metabolic Syndrome in a 22,892 Japanese Population and Its Associations with Life Style

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Mitsuyoshi Urashima,*1 Takashi Wada,*2 Tsutomu Fukumoto,*2 Mari Joki,*2
Toshihiko Maeda,*2 Hiroko Hashimoto,*2 Sai Oda*2

Abstract

Background In April 2005, the Japanese Society of Internal Medicine, in collaboration with seven other Japanese societies, defined the diagnostic criterion for Japan-specific metabolic syndrome (J-MS). We then investigated the prevalence of J-MS compared to MS as defined by the US National Cholesterol Education Program (U-MS). We also investigated J-MS and U-MS's association with life style and family history in the Japanese population.

Methods The subjects comprised of 22,892 Japanese who visited the Health Science Center at Jikei University Hospital in Tokyo Japan for medical check-ups between January 2000 and December 2004. In addition to medical check-ups at the center, participants completed a simple, self-administered questionnaire on life style and family history, the answers to which were later confirmed through interviews with medical doctors.

Results The age- and gender-standardized prevalence of J-MS and U-MS in the general Japanese population using Japan's 2001 National Census data was 8.4% and 5.3%, respectively. Multiple logistic regression analyses demonstrated that family histories of hypertension/diabetes, smoking habits, alcohol consumption (>150g of ethanol index/weeks), eating out in the evening, faster eating speed, larger portion size, and a diet high in animal fats were positively related to J-MS, whereas a balanced diet, brisk walking, regular exercise and working 3–7 hours per day were negatively associated with the prevalence of J-MS.

Conclusion These results suggest that the prevalence of MS amongst Japanese may be associated with life style factors such as smoking, size of food portions and alcohol consumption, as well as with family history of hypertension and diabetes.

Key words Metabolic syndrome, Life style, Family history, Obesity, Dyslipidemia

Introduction

Some metabolic abnormalities including glucose intolerance, central obesity, dyslipidemia and hypertension co-occur in an individual as metabolic syndrome (MS), which is associated with an increased risk of cardiovascular diseases.[1–4] The existence of MS had been widely recognized for a long time under different names.[5,6] While the overall concept of MS was generally acknowledged, there has been no commonly accepted definition of MS. In 1999, the World Health Organization (WHO) developed the first internationally recognized definition of MS.[7,8] Then, in 2001, the US National Cholesterol Education Program (NCEP) specified the criterion for MS (henceforth U-MS) as the presence

*1 Division of Clinical Research and Development, Jikei University School of Medicine, Tokyo
*2 Health Science Center, Jikei University School of Medicine, Tokyo
Correspondence to: Mitsuyoshi Urashima MD, PhD, MPH, Division of Clinical Research and Development, Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan.
Tel: 81-3-3433-1111, Fax: 81-3-5400-1250, E-mail: urashima@jikei.ac.jp

of at least three conditions from following five components: 1) abdominal obesity; 2) hypertriglyceridemia; 3) low high-density lipoprotein cholesterol (HDL-C); 4) high blood pressure; 5) high fasting glucose.[9]

Yet, the extent of obesity associated with increased risk differs according to ethnicity and lower cutoff points were suggested for Asians.[10] In April 2005, a committee of specialists from eight Japan Societies: the Japan Society for the Study of Obesity; the Japan Atherosclerosis Society; the Japan Diabetes Society; the Japanese Society of Hypertension; the Japanese Circulation Society; the Japanese Society of Nephrology; the Japanese Society on Thrombosis and Hemostasis; the Japanese Society of Internal Medicine[11] specified a diagnosis criterion of Japan-specific metabolic syndrome (J-MS) appropriate for Japanese. According to the criterion of J-MS, abdominal obesity: waist circumstance: ≥85 cm in men and ≥90 cm in women was obligatory since central obesity, as opposed to body mass index, may reflect the volume of fat around visceral organs. This is one of the main aspects in which J-MS differs from the criterion specified by the NCEP. In addition to abdominal obesity, the presence of two of the following three abnormalities must be observed in order to confirm a diagnosis of J-MS: dyslipidemia: hypertriglyceridemia or low HDL-C; hypertension; hyperglycemia.

In this study, we aimed to identify the prevalence of MS defined both according to the Japanese criterion and that defined by the NCEP in the same 22,892 subjects who visited a university hospital for medical check-up. We sought to identify associations between MS generally, and both life style factors and family history using multiple logistic regression analyses.

Participants and Methods

Population

The subjects comprised 22,892 Japanese, aged 20 to 93 years old, (16,535 males (72.2%), mean age 47.9 ± 10.7 years and 6,357 females: mean age 44.6 ± 11.2 years), who visited the Health Science Center at Jikei University Hospital in the center of Tokyo, Japan, between January, 2000 and December, 2004, for medical check-ups. Of subjects who attended more than twice during the study period, only data from the last visit were used. Subjects whose age was less than 20 years old were excluded.

Variables

All participants completed a simple, self-administered questionnaire (in Japanese) regarding life style and family history, among the subject's parents and brothers/sisters, of cardiovascular diseases in addition to dyslipidemia, hypertension or diabetes mellitus. Following this short questionnaire, anthropometrical examination including height, weight and waist circumference measurements, was performed by trained staff. Blood samples were collected after an overnight fast (no food intake for more than 12 hours). After these examinations, the medical doctor interviewed subjects to confirm their answers to the questionnaires.

Outcome measures

The primary outcome was MS according to the criterion defined by the Japanese societies' committee (J-MS).[11] Abdominal obesity: waist circumstance: ≥85 cm in men and ≥90 cm in women was obligatory for a diagnosis of MS. In addition to abdominal obesity, any two of the following three abnormalities should be observed: A: dyslipidemia: triglyceride (TG) ≥150 mg/dl or HDL-C <40 mg/dl or use of anti-dyslipidemia medication; B: hypertension: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of antihypertensive medication; C: hyperglycemia: fasting plasma glucose ≥110 mg/dl or use of hypoglycemic medication.

To enable comparisons with reports in other countries, we also applied criterion set by the US NECP, described here as U-MS, according to the presence of three or more of the following five components: 1) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; 2) hypertriglycemia: TG 150 mg/dl; 3) HDL-C: <40 mg/dl in men and <50 mg/dl in women; 4) blood pressure: 130/85 mmHg or use of antihypertensive medication; 5) high fasting plasma glucose: 110 mg/dl or use of hypoglycemic medication.[9]

Statistics

Multiple logistic regression analyses were applied to detect important variables linked to the incidence of MS. The prevalence of MS in the

Table 1 Prevalence of metabolic syndrome (J-MS and U-MS) in different gender and age groups

		Total N=22,892	20≦age<30 N=563	30≦age<40 N=6,573	40≦age<50 N=6,623	50≦age<60 N=5,906	60≦age<70 N=2,707	70≦age N=520	Adjusted %[*12]
AO[*1]	male	7,926 (47.9)[*12]	81 (28.8)	1,690 (39.2)	2,359 (48.9)	2,462 (53.8)	1,125 (51.4)	209 (59.5)	46.2
	female	625 (9.8)	29 (10.3)	177 (7.8)	144 (8.0)	156 (11.7)	81 (15.7)	38 (22.5)	12.3
	total	8,551 (37.4)	110 (19.5)	1,867 (28.4)	2,503 (37.8)	2,618 (44.3)	1,206 (44.6)	247 (47.5)	29.1
AO+DL[*2]	male	3,422 (20.7)	33 (11.7)	732 (17.0)	1,099 (22.8)	1,051 (23.0)	430 (19.6)	77 (21.9)	19.2
	female	128 (2.0)	1 (0.4)	18 (0.8)	26 (1.5)	39 (2.9)	29 (5.6)	15 (8.9)	3.1
	total	3,550 (15.5)	34 (6.0)	750 (11.4)	1,125 (17.0)	1,090 (18.5)	459 (17.0)	92 (17.7)	11.1
AO+HT[*3]	male	3,208 (19.4)	14 (5.0)	378 (8.8)	837 (17.3)	1,173 (25.6)	662 (30.2)	144 (41.0)	20.1
	female	201 (3.2)	0 (0.0)	22 (1.0)	39 (2.2)	70 (5.3)	41 (7.9)	29 (17.2)	5.2
	total	3,409 (14.9)	14 (2.5)	400 (6.1)	876 (13.2)	1,243 (21.1)	703 (26.0)	173 (33.3)	12.6
AO+HG[*4]	male	1,719 (10.4)	2 (0.7)	158 (3.7)	420 (8.7)	700 (15.3)	362 (16.5)	77 (21.9)	10.5
	female	85 (1.3)	0 (0.0)	10 (0.4)	16 (0.9)	36 (2.7)	13 (2.5)	10 (5.9)	2.0
	total	1,804 (7.9)	2 (0.4)	168 (2.6)	436 (6.6)	736 (12.5)	375 (13.9)	87 (16.7)	6.2
AO+DL +HT	male	1,509 (9.1)	6 (2.1)	194 (4.5)	456 (9.4)	536 (11.7)	264 (12.1)	53 (15.1)	8.8
	female	65 (1.0)	0 (0.0)	4 (0.2)	10 (0.6)	24 (1.8)	16 (3.1)	11 (6.5)	1.9
	total	1,574 (6.9)	6 (1.1)	198 (3.0)	466 (7.0)	560 (9.5)	280 (10.3)	64 (12.3)	5.6
AO+DL +HG	male	908 (5.5)	2 (0.7)	93 (2.2)	255 (5.3)	370 (8.1)	153 (7.0)	35 (10.0)	5.3
	female	36 (0.6)	0 (0.0)	4 (0.2)	4 (0.2)	14 (1.1)	8 (1.6)	6 (3.6)	1.0
	total	944 (4.1)	2 (0.4)	97 (1.5)	259 (3.9)	384 (6.5)	161 (6.0)	41 (7.9)	3.2
AO+HT +HG	male	976 (5.9)	1 (0.4)	54 (1.3)	224 (4.6)	407 (8.9)	233 (10.6)	57 (16.2)	6.4
	female	53 (0.8)	0 (0.0)	3 (0.1)	6 (0.3)	27 (2.0)	8 (1.6)	9 (5.3)	1.4
	total	1,029 (4.5)	1 (0.2)	57 (0.9)	230 (3.5)	434 (7.4)	241 (8.9)	66 (12.7)	3.9
AO+DL +HT+HG	male	531 (3.2)	1 (0.4)	37 (0.9)	141 (2.9)	225 (4.9)	102 (4.7)	25 (7.1)	3.3
	female	22 (0.4)	0 (0.0)	1 (0.0)	1 (0.1)	11 (0.8)	4 (0.8)	5 (3.0)	0.7
	total	553 (2.4)	1 (0.2)	38 (0.6)	142 (2.1)	236 (4.0)	106 (3.9)	30 (5.8)	2.0
J-MS[*5]	male	2,331 (14.1)[*3]	7 (2.5)	267 (6.2)	653 (13.5)	863 (18.9)	446 (20.4)	95 (27.1)	14.0
	female	110 (1.7)	0 (0.0)	9 (0.4)	18 (1.0)	43 (3.2)	24 (4.6)	16 (9.5)	2.9
	total	2,441 (10.7)	7 (1.2)	276 (4.2)	671 (10.1)	906 (15.3)	470 (17.4)	111 (21.4)	8.4
U-AO[*6]	male	501 (3.0)	14 (5.0)	138 (3.2)	138 (2.9)	131 (2.9)	61 (2.8)	19 (5.4)	3.6
	female	724 (11.4)	30 (10.6)	191 (8.4)	167 (9.3)	194 (14.6)	100 (19.3)	42 (24.9)	14.1
	total	1,225 (5.4)	44 (7.8)	329 (5.0)	305 (4.6)	325 (5.5)	161 (6.0)	61 (11.7)	8.9
U-TG[*7]	male	4,365 (26.4)	43 (15.3)	1,016 (23.6)	1,457 (30.2)	1,291 (28.2)	497 (22.7)	61 (17.4)	23.1
	female	340 (5.4)	3 (1.1)	53 (2.3)	91 (5.1)	116 (8.7)	55 (10.6)	22 (13.0)	6.6
	total	4,705 (20.6)	46 (8.2)	1,069 (16.3)	1,548 (23.4)	1,407 (23.8)	552 (20.4)	83 (16.0)	14.8
U-HDL[*8]	male	1,433 (8.7)	19 (6.8)	399 (9.3)	419 (8.7)	382 (8.4)	184 (8.4)	30 (8.6)	8.3
	female	465 (7.3)	10 (3.6)	116 (5.1)	144 (8.0)	109 (8.2)	67 (13.0)	19 (11.2)	8.0
	total	1,898 (8.3)	29 (5.2)	515 (7.8)	563 (8.5)	491 (8.3)	251 (9.3)	49 (9.4)	8.2
U-BP[*9]	male	5,108 (30.9)	28 (10.0)	643 (14.9)	1,247 (25.8)	1,865 (40.8)	1,100 (50.2)	225 (64.1)	32.4
	female	886 (13.9)	1 (0.4)	88 (3.9)	171 (9.5)	338 (25.4)	181 (35.0)	107 (63.3)	21.5
	total	5,994 (26.2)	29 (5.2)	731 (11.1)	1,418 (21.4)	2,203 (37.3)	1,281 (47.3)	332 (63.9)	26.9
U-PG[*10]	male	2,672 (16.2)	4 (1.4)	229 (5.3)	635 (13.2)	1,088 (23.8)	605 (27.6)	111 (31.6)	16.2
	female	306 (4.8)	0 (0.0)	29 (1.3)	71 (4.0)	110 (8.3)	59 (11.4)	37 (21.9)	7.3
	total	2,978 (13.0)	4 (0.7)	258 (3.9)	706 (10.7)	1,198 (20.3)	664 (24.5)	148 (28.5)	11.7
U-MS[*11]	male	1,060 (6.4)	6 (2.1)	142 (3.3)	292 (6.1)	389 (8.5)	197 (9.0)	34 (9.7)	6.2
	female	193 (3.0)	0 (0.0)	17 (0.8)	43 (2.4)	73 (5.5)	42 (8.1)	18 (10.7)	4.4
	total	1,253 (5.5)	6 (1.1)	159 (2.4)	335 (5.1)	462 (7.8)	239 (8.8)	52 (10.0)	5.3

[*1]: AO: abdominal obesity: waist circumstance: ≥85 cm in men and ≥90 cm in women [*2]: DL: dyslipidemia: triglyceride (TG) ≥150 mg/dl or HDL-C <40 mg/dl or use of anti-dyslipidemia medication [*3]: HT: hypertension: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of antihypertensive medication [*4]: HG: hyperglycemia: fasting plasma glucose ≥110 mg/dl or use of hypoglycemic medication [*5]: J-MS: Metabolic syndrome defined by Japanese Societies committee: AO+DL+HT; AO+DL+HG; AO+HT+HG; AO+DL+HT+HG. [*6]: U-AO: abdominal obesity: waist circumference >102 cm in men and >88 cm in women [*7]: U-TG: Hypertriglycemia: TG≥150 mg/dl [*8]: U-HDL: HDL-C: <40 mg/dl in men and <50 mg/dl in women [*9]: U-BP: blood pressure: 130/85 mmHg or use of antihypertensive medication [*10]: U-PG: high fasting glucose: 110 mg/dl or use of hypoglycemic medication [*11]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP): three and more from U-AO, U-TG, U-HDL, U-BP, U-PG, U-MS. [*12]: absolute number (%): adjusted: percentage was adjusted by age and gender in the Japanese general population using the 2001 National Census data.

Table 2 Risk of metabolic syndrome and family history of diseases: OR (95% CI)[*1]

	Cerebral infarction and/or bleeding	Hypertension	Coronary artery disease	Dyslipidemia	Diabetes mellitus[*2]
	1,820 (8.0)	6,386 (27.9)	1,258 (5.5)	855 (3.7)	3,345 (14.6)
J-MS[*3]	1.04 (0.90–1.20)	1.46 (1.32–1.60)[‡]	1.12 (0.94–1.34)	1.22 (0.97–1.54)	1.28 (1.14–1.44)[‡]
U-MS[*4]	1.04 (0.86–1.27)	1.41 (1.25–1.59)[‡]	1.02 (0.81–1.30)	1.40 (1.06–1.86)[†]	1.52 (1.32–1.76)[‡]

[*1]: OR and 95% CI of MS were computed with logistic regression analyses using each disease adjusted by age and gender. [*2]: Diabetes mellitus at least one in subject's parents or brothers/sisters [*3]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*4]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) [†]: $P<0.05$, [‡]: $P<0.005$

Japanese population as a whole was adjusted by distribution of age groups and gender using Japan's 2001 National Census data. Risks of MS associated with age/gender and life style/family history were shown as a risk ratio or odds ratio (OR) with 95% confidence interval (95% CI). All statistical analyses were performed with STATA 8.0 software (STATA Corporation, College Station, TX).

Results

Prevalence of MS in Japanese population

In total, 2,441 (10.7%) and 1,253 (5.5%) of subjects satisfied the criterion of J-MS and U-MS, respectively (Table 1). The age- and gender-standardized prevalence of J-MS and U-MS in the general Japanese population using the 2001 National Census data was 8.4% (95% CI: 8.2–8.6%) and 5.3% (95% CI: 5.1–5.4%), respectively. The standardized J-MS was quite different between men (14.0%, 95% CI: 13.7–14.3%) and women (2.9%, 95% CI: 2.7–3.0%) ($P<0.01$), in contrast, the standardized U-MS was closer between men (6.2%, 95% CI: 6.0–6.4%) and women (4.4%, 95% CI: 4.2–4.6%) ($P<0.01$).

The prevalence of J-MS and U-MS increased with age in both men and women. There was a 17.2-fold (95% CI: 8.1–36.5) and 9.4-fold (95% CI: 4.1–21.7) increase in risk ratio for having J-MS and U-MS in the age group ≥70 years old compared with that of 20–29 years old, respectively.

The criterion for J-MS was based on three components of the syndrome and percentages adjusted by age and gender were as follows: 1) dyslipidemia + hypertension + abdominal obesity (5.6%); 2) dyslipidemia + hyperglycemia + abdominal obesity (3.2%); 3) hypertension + hyperglycemia + abdominal obesity (3.9%); 4) dyslipidemia + hypertension + hyperglycemia + abdominal obesity (2.0%).

The criterion for U-MS had five components of the syndrome and percentages adjusted by age and gender was as follows: abdominal obesity (8.9%); elevated TG levels (14.8%); low HDL-C levels (8.2%); hypertension (26.9%); hyperglycemia (11.7%). Percentages adjusted by age and gender having three, four and five components in U-MS were 4.3%, 0.9% and 0.1%, respectively.

Family history associated with prevalence of MS

Associations between family histories of cardiovascular disease: cerebral infarction/cerebral bleeding excluding brain injury; hypertension; coronary artery disease; dyslipidemia; diabetes mellitus; and prevalence of J-MS and U-MS were investigated by adjusting for age and gender (Table 2). Family histories of hypertension and diabetes showed significant associations with the prevalence of both J-MS and U-MS ($P<0.005$). Family history of dyslipidemia was only associated with U-MS ($P<0.05$).

Life styles associated with prevalence of MS

Each component of life style: alcohol consumption; smoking habits; eating habits; exercise habits; work patterns; was examined in association with the prevalence of J-MS and U-MS adjusting for age and gender using multiple logistic regression analyses. Compared with those that drink least (alcohol index: <150 g of ethanol/week), there was a significant increase in risk of both J-MS and U-MS in the moderate range (151–450 g/week) and high range (≧451 g/week) (Table

Table 3 Risk of metabolic syndrome and alcohol consumption: OR (95% CI)[*1]

	Alcohol index[*2]		
	0–150 g/week N = 14,802	151–450 g/week N = 6,975	451– g/week N = 1,115
J-MS[*3]	1	1.31 (1.20–1.44)‡	1.94 (1.66–2.89)‡
U-MS[*4]	1	1.20 (1.05–1.38)†	1.69 (1.36–2.10)‡

[*1]: OR with 95% CI of MS was calculated for alcohol index: 151–450 g/week and 451≦g/week in comparison with 0–150 g/week using multiple logistic regression analysis adjusted by age and gender. [*2]: Information about alcohol consumption was elicited using the questionnaire item: "How many times a week on average do you drink alcohol, what kinds of alcohol, and how many glasses of each kind?" Answers were confirmed by a doctor. Then, amounts of ethanol were calculated as alcohol index: amount of alcohol consumption (g)/week × 0.8 = ethanol consumption (g)/week. [*3]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*4]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) †: $P<0.05$, ‡: $P<0.005$

Table 4 Risk of metabolic syndrome and smoking habits: OR (95% CI)[*1]

	Smoking habits[*2]		
	Non smoker N = 6,870	Recent smoker N = 7,638	Past smoker N = 8,384
J-MS[*3]	1	1.20 (1.07–1.35)‡	1.21 (1.08–1.37)‡
U-MS[*4]	1	1.21 (1.05–1.41)†	1.02 (0.87–1.20)

[*1]: OR with 95% CI of MS was calculated for 'recent smoker' and 'past smoker' in comparison with 'non smoker' using multiple logistic regression analysis adjusted by age and gender. [*2]: Information about smoking habits was elicited using questionnaire item: "Do you currently smoke, do you almost never smoke, or are you an ex-smoker?" Answers were confirmed by a doctor. [*3]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*4]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) †: $P<0.05$, ‡: $P<0.005$

3). Regarding smoking habits, the prevalence of MS was higher in both current and ex-smokers compared with non-smokers (Table 4). As for eating habits, subjects who answered 'Yes' to the question "Do you eat balanced daily meals?" had a negative correlation whereas subjects that answered 1+ days to the question "How many days per week on average do you eat out in the evening?" and subjects who answered 'Yes' to the question "Do you think you eat faster than others when eating alone?" both had positive associations with J-MS (Table 5A). In addition, subjects who answered 'Yes' to the question "Do you have enough vegetables and/or seaweed and/or mushrooms?" and who answered 1+ days to the question "How many days per week do you have breakfast?" had negative correlations whereas answers 'Yes' to the question "Do you eat between meals and/or eat late-night snacks?" were positively associated with the U-MS (Table 5A). We also investigated size of food portions and subjects' food preferences (Table 5B). Apart from the question "Do you think you consume more sweet foods and/or soft drinks than others?" both J-MS and U-MS were more prevalent in subjects who answered 'Yes' to the questions: "Do you think you eat too much?" "Do you prefer salty food?" "Do you think you eat more animal fat than others?" For exercise habits and physical activity, subjects who answered 'Yes' to the question "Do you try to do brisk walking for 1 hour or more per day?" and subjects who answered 'Yes' to the question "Do you regularly do vigorous exercise for 1 hour or more per week?" had negative associations with J-MS and U-MS prevalence (Table 6). In terms of

Table 5A Risk of metabolic syndrome and eating habits: OR (95% CI)[*1]

	Eating habits[*2]					
	Balanced meal[*3]	Enough vegetables[*4]	Breakfast[*5] (Days)	Eat out in the evening[*6] (Days)	Eating between meals[*7]	Fast eater[*8]
	Yes 15,561 (68.2)	Yes 7,039 (30.8)	Frequency per week Median: 7 days Mean ± SD: 5.6 ± 2.1	Frequency per week Median: 1 day Mean ± SD: 1.9 ± 1.8	Yes 8,873 (38.8)	Yes 11,584 (50.7)
J-MS[*9]	0.74 (0.66–0.82)‡	1.00 (0.90–1.11)	1.00 (0.98–1.02)	1.06 (1.03–1.09)‡	1.02 (0.93–1.13)	1.84 (1.68–2.01)‡
U-MS[*10]	0.65 (0.57–0.74)‡	0.83 (0.73–0.95)‡	0.97 (0.94–0.99)†	1.09 (1.06–1.13)‡	1.21 (1.08–1.38)‡	1.84 (1.63–2.08)‡

[*1]: OR and 95% CI of MS in association with specific eating habits was computed with multiple logistic regression analysis using six variables related with eating habits adjusted by age and gender. [*2]: Information about eating habits was elicited using questionnaire. A doctor subsequently confirmed subjects responses to the following items: [*3]: "Do eat a balanced daily meal?" Yes/No answer [*4]: "Do eat enough vegetables and/or seaweed, and/or mushroom?" Yes/No answer [*5]: "How many days per week do you have breakfast?" 0–7 days/week answer [*6]: "How many days per week on average do you eat out in the evening?" 0–7 days/week answer [*7]: "Do you eat between meals and/or eat late-night snacks?" Yes/No answer [*8]: "Do you think you eat faster than others?" Yes/No answer [*9]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*10]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) †: $P<0.05$, ‡: $P<0.005$

Table 5B Risk of metabolic syndrome and eating habits: OR (95% CI)[*1]

	Eating habits[*2]			
	Large portions[*3]	Salty food[*4]	More animal fat[*5]	More sweet foods including soft drinks[*6]
	Yes N = 6,513 (28.5%)	Yes N = 6,749 (29.5%)	Yes N = 5,332 (23.3%)	Yes N = 4,823 (21.1%)
J-MS[*7]	2.21 (2.01–2.42)‡	1.18 (1.08–1.30)‡	1.50 (1.35–1.66)‡	0.97 (0.86–1.09)
U-MS[*8]	2.07 (1.84–2.34)‡	1.17 (1.03–1.32)†	1.42 (1.23–1.62)‡	1.08 (0.94–1.25)

[*1]: OR and 95% CI of MS in association with specific eating habits was computed with multiple logistic regression analysis using four variables related with eating habits adjusted by age and gender. [*2]: Information about eating habits was elicited using questionnaire. A doctor subsequently confirmed subjects responses to the following items: [*3]: "Do you think you eat too much?" Yes/No answer [*4]: "Do you prefer salty food?" Yes/No answer [*5]: "Do you eat animal fat more often than others?" Yes/No answer [*6]: "Do consume more sweet foods including soft drinks than others?" Yes/No answer [*7]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*8]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) †: $P<0.05$, ‡: $P<0.005$

Table 6 Risk of metabolic syndrome and exercise habits: OR (95% CI)[*1]

	Exercise habits[*2]	
	Brisk walking 1+ hours per day[*3]	Regular vigorous exercise 1+ hours per week[*4]
	Yes N = 2,906 (12.7%)	Yes N = 7,955 (34.8%)
J-MS[*5]	0.75 (0.66–0.86)‡	0.79 (0.72–0.87)‡
U-MS[*6]	0.76 (0.64–0.91)‡	0.72 (0.63–0.81)‡

[*1]: OR and 95% CI of MS were computed with multiple logistic regression model using two answers to the questionnaire items concerning exercise habits adjusted by age and gender. [*2]: Information about exercise habits was elicited using questionnaire. A doctor subsequently confirmed subjects responses to the following items: [*3]: Do you do brisk walking for 1 hour or more per day? Do you try to have time more than 1 hour per day for exercise of fast walking? Yes/No answer [*4]: Do you do vigorous exercise regularly for 1 hour or more per week? Yes/No answer [*5]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*6]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) ‡: $P<0.005$

Table 7 Risk of metabolic syndrome and working habits: OR (95% CI)[*1]

	Work-rest pattern[*2]					
	Average days off per month	Average hours sleep per day	Average working hours per day			
			0–2 hours/day	3–7 hours/day	8–13 hours/day	14 and more hours/day
	Mean 7.7±4.1 SD days	Mean 6.2±1.0 SD hours	N=728	N=2,227	N=17,459	N=2,107
J-MS[*3]	0.99 (0.98–1.00)	0.98 (0.93–1.03)	0.98 (0.83–1.17)	0.71 (0.59–0.86)‡	1	0.99 (0.83–1.17)
U-MS[*4]	0.98 (0.96–0.99)‡	0.94 (0.88–1.01)	1.00 (0.71–1.41)	0.82 (0.66–1.02)	1	0.87 (0.69–1.10)

[*1]: OR and 95% CI of MS were computed with multiple logistic regression model using four categories of average work hours including house work as well as average days off per month and average hours sleep per day adjusted by age and gender. [*2]: Information about work patterns was elicited using a questionnaire, and the answers were confirmed subsequently through an interview with a doctor. [*3]: J-MS: Metabolic syndrome defined by Japanese Societies committee [*4]: U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP) ‡: $P<0.005$

Table 8 Risk of metabolic syndrome and all variables measured in this study: OR (95% CI)[*1]

	J-MS[*2]	U-MS[*3]
Family history of cerebral infarction and/or bleeding	1.04 (0.88–1.22)	0.95 (0.76–1.19)
Family history of hypertension	1.40 (1.26–1.56)‡	1.24 (1.08–1.43)‡
Family history of coronary heart diseases	1.14 (0.94–1.38)	0.95 (0.72–1.25)
Family history of dyslipidemia	1.16 (0.89–1.51)	1.07 (0.76–1.51)
Family history of diabetes mellitus	1.19 (1.05–1.36)†	1.36 (1.15–1.61)‡
Non-smoker	1	1
Recent smoker	1.17 (1.03–1.33)†	1.17 (0.99–1.40)
Ex-smoker	1.18 (1.03–1.34)†	0.98 (0.82–1.18)
Alcohol index 0–150g	1	1
Alcohol index 151–450g	1.29 (1.16–1.43)‡	1.17 (1.01–1.36)†
Alcohol index 451–g	1.79 (1.50–2.14)‡	1.60 (1.27–2.05)‡
Balanced meal	0.80 (0.71–0.91)‡	0.76 (0.64–0.89)‡
Enough vegetables	1.02 (0.91–1.15)	1.04 (0.89–1.22)
Breakfast	1.01 (0.99–1.04)	1.02 (0.98–1.05)
Eating out in the evenings	1.04 (1.01–1.07)†	1.03 (0.99–1.07)
Eating between meals	0.99 (0.88–1.11)	1.10 (0.94–1.28)
Eating fast	1.64 (1.48–1.82)‡	1.74 (1.51–2.00)‡
Large portions	1.96 (1.76–2.18)‡	1.76 (1.53–2.03)‡
Salty food	1.07 (0.97–1.19)	1.09 (0.95–1.26)
More animal fat	1.31 (1.17–1.47)‡	1.23 (1.05–1.44)†
Sweet food/drinks	0.92 (0.79–1.07)	1.01 (0.83–1.22)
Brisk walking 1+ hrs p/day	0.74 (0.64–0.87)‡	0.80 (0.65–0.98)†
Regular vigorous exercise 1+ hrs p/week	0.84 (0.75–0.93)‡	0.77 (0.66–0.89)†
Days off p/mth	0.99 (0.98–1.01)	0.99 (0.97–1.01)
Hours sleep per day	1.02 (0.97–1.08)	0.98 (0.91–1.06)
Work per day (0–2 hours)	1.08 (0.79–1.48)	1.16 (0.78–1.73)
Work per day (3–7 hours)	0.77 (0.62–0.94)†	0.94 (0.73–1.22)
Work per day (8–13 hours)	1	1
Work per day (14– hours)	0.95 (0.79–1.15)	0.82 (0.63–1.07)

[*1]: OR and 95% CI of MS were computed with multiple logistic regression model with all variables used in previous tables adjusted by age and gender. [*2]: Logistic model for J-MS: Metabolic syndrome defined by Japanese Societies: $R^2=0.1381$ [*3]: Logistic model for U-MS: Metabolic syndrome by the US National Cholesterol Education Program (NCEP): $R^2=0.0778$ †: $P<0.05$, ‡: $P<0.005$

work habits, when work hours per day ranged between 8 and 13 hours, the prevalence of J-MS decreased (Table 7), whereas U-MS decreased with more days off per month (Table 7).

Multiple logistic regression analyses

Multiple logistic regression models for J-MS and U-MS were computed using the same variables as previous analyses adjusted by age and gender (Table 8). Subjects with family histories of hypertension/diabetes, who drink more than 450 g of ethanol per week, and who eat out for dinner more often, who answered 'Yes' to the question "Do you think you eat faster than others?" "Do you think you eat too much?" "Do you think you eat more animal fat than others?" were positively correlated, whereas subjects who answered 'Yes' to the question "Do you have a balanced daily meal?" and "Do you regularly do vigorous exercise for 1 hour or more per week?" were negatively associated with both J-MS and U-MS. In J-MS, recent and past smoking habits and medium to high alcohol consumption (>150 g of ethanol/week) were positively associated with J-MS. Moreover, subjects who answered 'Yes' to the question "Do you try to do more than 1 hour of exercise of fast walking per day?" and who worked 8 to 13 hours per day were negatively associated with J-MS.

Discussion

Using data from the Health Science Center at Jikei University Hospital, we estimated the prevalence of J-MS and U-MS as 8.4% and 5.3% respectively in the general Japanese population older than 20 years, standardized by age and gender using Japan's 2001 National Census data.

In contrast to our data, MS as defined by WHO and NCEP typically affects 20–30% of the adult population in the USA[12–14] and Europe.[15] Mexican Americans have the highest age-adjusted prevalence of U-MS (31.9%).[12] In China, the age-standardized prevalence of U-MS was 9.8% in men and 17.8% in women.[16] Thus, the prevalence of MS in Japan appears to be lower than that in other countries. However, since the center where study was done is located in the center of Tokyo, these percentages may be specific to the local population, which has a relatively high socioeconomic level, and healthier behavior and/or longer work hours than the population as a whole. Thus, random sampling from across Japan is required before a conclusive statement can be made about the low prevalence of MS in Japan compared to other countries.

Our study revealed a higher prevalence of J-MS (8.4%) than U-MS (5.3%) using data obtained from the same subjects. The major difference between J-MS and U-MS is the cutoff point of waist circumstances: J-MS: ≥85 cm in men; ≥90 cm in women; U-MS: >102 cm in men and >88 cm in women. As morbidity and mortality from cardiovascular diseases occurs in people with lower body mass indexes and smaller waist circumferences in Asian populations, the commonly used definitions of MS, at least in their present forms, have limited clinical usefulness for Asian populations and may need some ethnic group-specific modifications for global use.[10,17] In fact, abnormal waist circumference was considerably more prevalent among individuals with MS in the US (72% in men, 94% in women) compared with their Asian counterparts, but substantial variation was also observed even among the Asian population (13–22% in men, 38–63% in women).[18] Therefore, the cutoff points were set lower in J-MS than in U-MS. However, these waist circumferences are provisional pending validation through follow-up studies.

Both J-MS and U-MS were associated with family histories of hypertension and diabetes.

In contrast, there was no significant association with family histories of cerebral infarction/bleeding or coronary artery disease. The prevalence of infarction/bleeding and coronary artery disease in association with MS is less than that of hypertension and diabetes, which may make statistical significance difficult to detect. Thus, research using larger sample populations is required to establish the association between family history of cerebral infarction/bleeding or coronary artery disease and MS with any reliability.

Few studies have examined the risk of MS and family history.[19,20] Susceptibility to MS has recently been linked with a mitochondria-DNA variant.[21,22] However, life style factors remained significant even when adjustments for family history were made in the multivariate analyses. Thus, examining genetic and life style factors simultaneously may be important for future studies.

In addition to factors of familial aggregation, life style factors were associated with the prevalence of MS. Japanese migrants and their descendants in Brazil have been shown to be at high risk for components of MS.[23,24] However, randomized trials have shown that changes in life style can decrease the risk of MS.[25] We investigated the life style components of alcohol, smoking, diet, exercise, and work, using cross sectional design and questionnaires. Smoking and alcohol consumption was linked to a higher prevalence of MS in this study, consistent with previous articles.[26–29] In this study, a healthy diet, identified in terms of balanced, regular meals at home, smaller portions, and less salty food and animal fat, was significantly linked with a reduced risk of MS. Dietary pattern has been empirically shown to effect the development of MS.[30,31] In this study, behavior associated with fitness was also shown to decrease the risk of MS, which is also consistent with previous knowledge.[32,33] Similarly, efforts to lessen the amount of time spent watching television or videos or using a computer, especially if coupled with increases in physical activity, could result in substantial decreases in the prevalence of MS.[34] In terms of work, 3–8 hours work per day was associated with a lower MS prevalence. In other words, working either too little or too much (see Table 7) is not good for the health, assuming no bias and adjustment. Moreover, taking enough days off is also associated with a lower incidence of MS. Although there are already a few reports about associations between work patterns and MS prevalence,[35] this represents another interesting area for future research in this field.

These results suggest that the prevalence of MS in Japanese may be associated with life style factors of smoking, food intake and alcohol consumption, exercise and rest as well as with family history of hypertension and diabetes, which is consistent with the healthy habits "None of one, less of two, more of three".[36,37]

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Review Article

Evidence-based Guidelines Needed on the Use of CT Scanning in Japan

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Nader Ghotbi,[*1,2] Mariko Morishita,[*1,2] Akira Ohtsuru,[*1] Shunichi Yamashita[*2,3]

Abstract

The increasing use of medical radiation, especially in diagnostic computed tomography (CT) scanning, has raised many concerns over the possible adverse effects of procedures performed without a serious risk versus benefit consideration, particularly in children. The growth in the number of CT scanning installations and usage, some new and unprecedented applications, the relatively wide variation of radiation doses applied by different radiological facilities, and the worrisome estimations of increased cancer incidence in more susceptible organs of children all point to the need for a clear specification of evidence-based guidelines to help limit and control the amount of radiation doses the Japanese population is being exposed to through medical diagnostic imaging technologies. Recommendations have already been issued on how to reduce the exposure dose to the minimum required especially in pediatric CT but more work is needed to establish good practice principles by the medical community through determination of more reasonable indications to request CT scanning.

Key words Computed tomography (CT) scanning, Evidence-based guidelines, Medical radiation, Pediatric CT, Radiation induced cancer

Introduction

The average annual collective doses of ionizing radiation exposure to the UK population from all sources have been summarized in a recent review[1] that depicts a good example of the latest situation of radiation exposure in developed countries. Radon as one of the natural sources of radiation, is responsible for 50% of the total annual dose (Fig. 1a) and next to it diagnostic radiology becomes the largest source of radiation exposure to the general population. The use of diagnostic X-rays also comprises more than 93% of all man-made sources of such exposure. On the other hand, the latest available data in Japan point to a much larger role of medical radiation in the average annual collective radiation doses (Fig. 1b).

The risk of cancer induction by medical radiation is not a recent issue but a long-standing one.[2] Fortunately, the radiation doses of all common diagnostic radiological examinations have generally been decreasing, except for computed tomography (CT) and interventional radiology (particularly angiography), which have increased. It is also worth noting that on an individual basis, the radiation dose a person receives during a CT examination is much higher than the expected dose of annual natural background radiation. Most of the recent increase in medical radiation dose has been ascribed to the higher frequency of use as well as higher radiation doses of CT scanning (Fig. 2).

*1 Department of International Hibakusha Medical Center, Nagasaki University Hospital, Nagasaki
*2 Department of Molecular Medicine, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki
*3 Radiation and Environmental Health, Department of the Protection of Environment, Sustainable Development and Healthy Environment, WHO/HQ, Geneva, Switzerland
Correspondence to: Nader Ghotbi MD, PhD, Department of Molecular Medicine, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki city 852-8523, Japan.
Tel: 81-95-849-7116, Fax: 81-95-849-7117, E-mail: naderq@hotmail.com

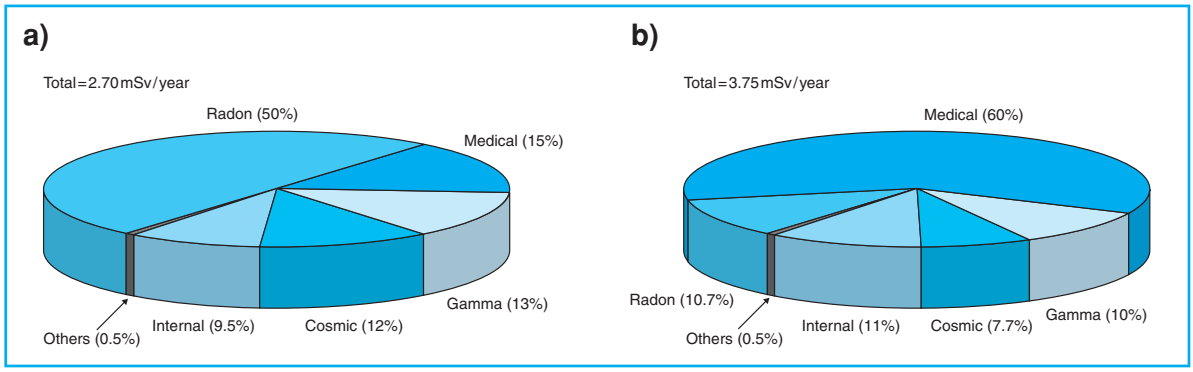

Fig. 1a) The most recent (2005) estimation of the average annual dose to the general population from all sources of ionizing radiation in UK is about 2.7 mSv, divided into five major & "other" sources (based on HPA-RPD-001 Report)

b) The 1992 estimation of the average annual dose to the general population from all sources of ionizing radiation in Japan was about 3.75 mSv, divided into five major & "other" sources (based on data of the Japanese Nuclear Safety Research Association)

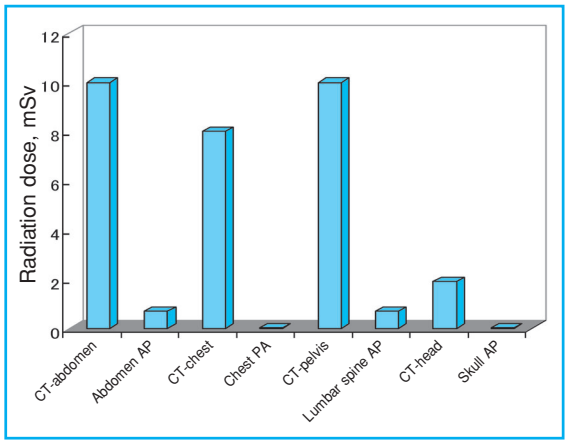

Fig. 2 Average effective radiation doses from diagnostic CT and the corresponding plain X-ray examinations to adults

Many physicians are unaware that CT examinations expose their patients to significantly higher radiation doses; dose of an abdominal CT is 400 times higher than a chest X-ray. (from Wall BF, Hart D. Revised radiation doses for typical X-ray examinations. BJR. 1997;70:437–439).

The growth of the radiation dosage ascribed to CT usage is mainly due to the increasing use of techniques such as contrast and multiphase enhancement, and multi-slice CT[3]; also the development of new helical CT has played a large role in the increase of pediatric CT usage because the fast spiral (helical) CT systems eliminated the need for sedation in most cases.[4,5] By the year 2000, US researchers reported an increase in the frequency of CT examinations to about 11% of all radiological examinations, accounting for 67% of the total effective dose from diagnostic radiology.[6]

In spite of several precautionary advisories that have already been published,[7–10] the increasing number of annually performed CT scans has moved far beyond control and has raised serious concerns over radiation safety, particularly induction of cancer. Radiation exposure through medical radiological devices has been blamed for 0.6% up to 1% (more than 3% for Japan) of total cancer incidence in many countries,[11,12] and specifically the risk of cancer induction through CT scans performed on children has received particular attention.[13–15] The extra concern over pediatric use of radiation is due to the fact that many organs in children are more sensitive to cancer induction. Also children receive a higher absorbed dose due to the small size of their body and with more years of life ahead for such a complication to appear, the lifetime risk of cancer is higher for them.[14,16]

There have been many attempts to lower the exposure dose of medical radiation,[17,18] either through guidelines for the radiological facilities to set dose parameters of their machines to the lowest needed range, or recommendations to physicians not to request high-dose diagnostic radiological examinations for their patients without a clear indication for its necessity and only after consideration of other diagnostic

Table 1 Mean effective dose to patients per procedure, from common CT scan examinations in some developed countries

Country	Year	Head CT	Chest CT	Abdomen CT
Japan	1994	—	4.6–10.8	6.7–13.3
Germany	1993	2.6	20.5	27.4
Australia	1995	2.6	10.4	16.7
United Kingdom	1994	1.6	9.7	12.0

(from UNSCEAR 2000 Medical radiation exposures, Annex D)

alternatives, such as ultrasound and MRI.

Unfortunately the number of peer-reviewed papers on the subjects of efficacy, dose and image quality criteria, especially for CT usage in children, is still limited; the lack of internationally approved indices for image quality and exposure among X-ray equipment manufactures is partly responsible for this problem. Still many radiological facilities purchase equipment on the basis of higher image quality, and/or operate their equipment in a high-dose, high-image quality mode.

In this paper, we will focus our attention on special precautions for CT scanning, especially in children, and will discuss the specific situation in Japan with regard to medico-radiological practice.

The Use of Diagnostic Radiology & CT Scanning in Japan

In Japan, according to UNSCEAR survey,[19] the annual frequency of diagnostic medical radiological examinations increased from 830 per 1,000 population in 1979, to 1,160 per 1,000 in 1990, and then to 1,477 per 1,000 population in 1996. However, a relatively significant part, namely 42% of the last figure, was related to chest X-rays which is a very low dose examination. This large share of chest X-rays in the number of annual radiological examinations in Japan, which is two times higher than in Germany at the same period (chest X-rays, 21%) can be explained by the Japanese anti-tuberculosis law that requires annual X-rays of students and employees over 16 years of age in the form of Mass Miniature Radiography (MMR).

Publication of guidelines, regulations and reference dosimetry for CT by European and international authorities cited earlier,[8–10] led the Japan Industry Association of Radiological Systems (JIRA) to respond by issuing some guidance and countermeasure recommendations to reduce the CT exposure dose.[20] Accordingly, CT manufacturers in Japan now provide data related to X-ray exposure dose including the weighted CT dose index (CTDIw) for adjusting CT exposure parameters as well as a CT infant protocol to reduce the dose for children. Moreover, the Japan Association of Radiological Technologists (JART) recently published a set of recommendations referred to as "pediatric CT guidelines to lower the dose of radiation" (http://www.jart.jp, in Japanese).

However, the observation of such standards of radio-diagnostic practice in Japan has not been mandatory or under the control of an agency (such as FDA in USA) and there are concerns that standards are not fully observed in some centers in order to achieve higher image resolution; the presence of a wide gap in the range of CT exposure doses in Japan (Table 1) raises the possibility that different facilities are not following the same standards. The publication of a paper that estimated the risk of cancer induced by diagnostic radiology in 15 countries and cited the highest risk for Japan,[11] reverberated through the Japanese radiological community. Although the basic assumption in this paper, namely the extension of the linear non-threshold (LNT) dose-effect relation to very low dose radiation, is still controversial[21–23] and the lowest doses of X-rays for which reasonably reliable evidence of increased cancer risk exists range from 10 to 50 mGy,[24] CT is not considered a low dose procedure (in 1998, the European Community classified CT as a high-dose procedure). Recently the in vivo formation

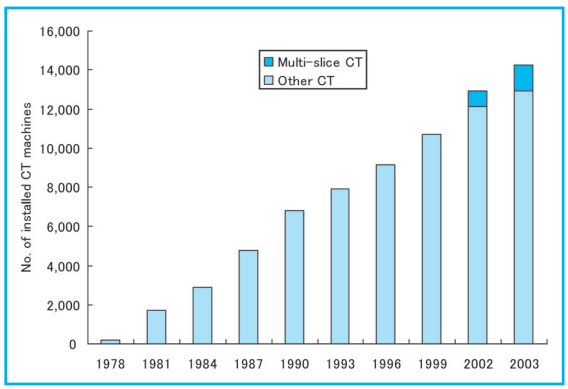

Fig. 3 Changes in the number of CT equipment installations in Japan through recent years

The number of Multi-slice CT machines in Japan reached 1,361 units in 2003. (from data presented by Nishizawa)

(and normally, repair) of DNA double strand breaks has been demonstrated after radiation doses in typical CT examinations.[25]

Some of the Japanese CT scan usage data are quite alarming. In Japan, there are no restrictions for CT use in cancer screening and routine health medical check-ups. Currently some medical imaging facilities are promoting new and unprecedented applications for CT scanning such as whole body CT scans combined with a PET examination, especially for cancer screening of asymptomatic individuals. With private radiological facilities openly advertising CT-PET full body screening to healthy people, and the only barrier being the cost of approximately US$1,100 which is not covered by health insurance, the commercialization of part of the medico-radiological sector has become a reality.

On the other hand, egalitarian public health policies to equip rural medical facilities with high-tech equipment such as CT machines in order to secure equal access to medical technologies all around Japan, have also been implicated.[26] These and other factors have been responsible for the growth of CT equipment installations in Japan (Fig. 3) such that the number of CT machines per million population of Japan was reported as 87.8 in 2000,[27] while Canada had only 10.3 CT machines per million population at the same period (CIHI report). The newer multi-slice CT machines expose the patients to about 40% higher radiation doses and in some applications a double dose or even higher.[28]

Our own survey on CT scanning usage in Nagasaki University Hospital (unpublished data) suggests that factors other than private economic gains may be responsible for overuse of CT in Japan, such as a lack of guidelines on clinical management and decision making, patients' expectations and physicians' over-reliance on high-tech imagery rather than clinical observation, which will be discussed further in our example of management of minor head trauma in children.

The Risks of Radiation Doses Used in CT

The lifetime cancer mortality risk from a single full-body CT examination has been estimated around 0.08% (about 1 in 1,250) for a 45-year-old adult,[29] but as mentioned earlier, the pediatric population is particularly susceptible to CT radiation doses. The thyroid gland, breasts and gonads in growing children are more sensitive to radiation meaning that the same radiation dose per unit weight of tissue is more prone to cancer in a child, compared with an adult.[14] Also, the smaller size of a child leads to the exposure of many nearby organs by CT slices of a nearby regional section, to a higher degree than an adult.[30] For example, the thyroid may be exposed in CT scan of the chest as well as the cervical and thoracic spines, the neck, and facial bones, and gonads in girls may be included in CT scans of abdomen as well as pelvis.

Calculations of Brenner et al. for "head" CT scans, show the risk of brain cancer to be the highest, with thyroid cancer posing a smaller risk of about 10% almost irrespective of sex, while in "abdominal" CT scans, stomach, liver and colon cancer dominate the risk profile which is higher for females. They estimated the lifetime cancer mortality risk attributable to radiation exposure from a single abdominal CT scan in a 1 year old child as about 1 in 550, and for a single head CT scan, 1 in 1,500.[13] These estimates are based on analyses of mortality data among Japanese atomic bomb survivors who were exposed to intermediate levels of radiation doses and therefore theoretically must be more applicable to the Japanese population. However, it must be emphasized that such a small increase over the background risk of cancer is still too small to be detected in an epidemiologic study.

It is not only the risk of cancer, but also the possible effects of CT scans on the development

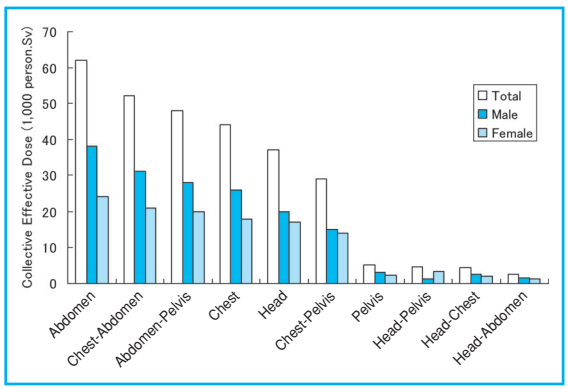

Fig. 4 Annual collective effective dose by the body regions CT scanned in Japan
(from Nishizawa et al. Nippon Acta Radialogica. 2004;64)

of cognitive capabilities of children,[31] that requires a reasonable risk versus benefit balance when ordering CT scans.

Overall, the raising of these concerns has caused many researchers and health care authorities to recommend strategies to minimize CT radiation exposure for children. The ALARA (As Low As Reasonably Achievable) principle is the basis of such strategies that aim to limit the CT examinations performed to only necessary ones, to limit the region of coverage, and to adjust individual CT dose settings based on indication, the region imaged, and size of the child.[32]

As for the scales of CT scanning practice in Japan, according to Nishizawa et al.,[27] the number of CT examinations per 1,000 population in Japan in the year 2000 was 290 and the average annual effective dose per caput was estimated as 2.3 mSv. About 3% (1.140.000) of all CT scans were performed on children (14 years old or less) 62% of which were performed on males; in comparison in those 15 years old and more, 54% were done on males. Eighty two percent of these examinations were head CT scans, compared with only 39% in the age group ≥15. Although "head" CT scans were the most common CT procedure, abdominal organs received the highest total collective doses in CT scans (Fig. 4). In the United States, according to the 2000–2001 NEXT survey[33] the total number of CT exams annually was about 58 million and the average effective dose per CT examination was approximately 6.2 mSv, so the average annual effective dose per caput was 1.2 mSv. The number of CT scans on children less than 15 years of age was estimated to be 2.7 million in the year 2000, about 4.8% of the total.[34]

Risk Versus Benefit of CT Examinations

Observation of exposure reduction principles in Japan has been recommended to all radiodiagnostic facilities but it is not mandatory.[35]

On the other hand, the justification of many of the CT scan requests is based on the assumption that the benefits are likely to exceed the risks, even though many physicians do not have a good knowledge of the amount of radiation exposure to the patients during radiological examinations.[36] For a risk versus benefit study, the radiation risks may be estimated from the effective dose using the system recommended by the International Commission on Radiological Protection, but the benefits of investigations in pediatric radiology are currently un-quantified. Benefits of some tests are so large that any further evaluation may be deemed unnecessary while for some others the maximum potential benefit is so low that they can be discarded. For most investigations, however, research into the magnitude of benefit to the patient is required in order to establish that it is greater than the magnitude of the radiation risk.[37] Increasing numbers of publications suggest more widespread use of CT as the primary imaging technique in multiple clinical scenarios, such as the child with abdominal pain, suspected appendicitis, or suspected renal calculi.[38,39]

For cases in which it is decided that the potential benefits from the information obtained on CT are greater than the risk of the radiation dose, technical factors can still be adjusted to minimize the radiation dose; this adjustment will be the responsibility of the radiologist supervising the examination.

The most recent study on the risks of exposure to low levels of radiation is further proof that concerns over CT scanning doses can be taken seriously[40]; this study on protracted exposures on an occupational basis also underscores the necessity of protecting physicians involved in sophisticated diagnostic and interventional radiological procedures,[41] including on how to monitor the exposure in the workplace, particularly in Japan.

Minor head trauma is one of the most

common reasons to refer children for a head CT scan, especially in Japan. Though minor head trauma in children is very common, it has a very low rate of complications which may be severe; and therefore clinical guidelines have been recommended to help with its correct management.[42] Compared with the UK, Canada,[43] and the USA[44] where there are a series of guidelines for the use of CT scanning in the workup of head injuries in both adults and children, such as those of the Royal College of Surgeons of England and the National Institute of Clinical Excellence (NICE) in the UK,[42] medical doctors in Japan rely mainly on their individual clinical judgment.

Although pediatricians should have the primary and pivotal role in the management of minor head trauma in children, in our survey at Nagasaki University Hospital, neurosurgeons commonly take over this responsibility from the beginning. This is while less than 1 in 5,000 patients without a loss of consciousness sustain intracranial injuries and only 2% to 5% of those with loss of consciousness may require neurosurgical intervention. In a relatively large epidemiological study in Germany, it was noted that while on average a CT scan was taken in only 13.4% of pediatric head trauma cases, the children treated by neurosurgeons received a CT in 75% of the cases.[45]

From the standpoint of health policy making, the potential risk calculated with linear extrapolations from higher doses can be justified even if too conservative because they probably represent the best interest of protecting patients.[46] On the other hand, radiation risk issues are still not taken into account in many papers on clinical decision-making. An example is a WHO collaborative study, which takes a more relaxed position on CT requests for minor head trauma in children, stating that clinical factors can hardly predict CT scan abnormalities and the need for intervention.[47]

Conclusions

The role of ionizing radiation in the promotion of human health is very similar to a double-edged sword. The radiation safety and risk-benefit ratio of various interventional radiological procedures, especially those with a higher dose of radiation such as CT scanning, need a fairly critical evaluation.

In developed countries such as Japan, more concrete evidence should be collected and evaluated on the safety and benefits versus the hazards of common CT applications, especially in the field of pediatrics. The increasing number of CT scan examinations has become a source of concern of the risk of cancer and/or deleterious effects on cognitive function in children. New and more comprehensive guidelines are needed to recommend good practice points to radiological facilities and all physicians who perform or request radiological procedures in Japan.

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Developing Urban Infrastructure Supportive to Health: The Healthy Cities approach

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Takehito Takano*1

Abstract

As a result of the population increase in urban areas globally, urban living environments and living conditions and their relation to human health have become a serious concern. A national effort—Healthy Japan 21—emphasizes the importance of creating a 'health-supportive environment' in addition to improving individuals' own efforts towards living healthily. The concept of how human health can be supported by the provision of an appropriate living environment is based on a model of stages of medicine proposed by McDermott. Research results on how urban green spaces contribute to the longevity of urban senior citizens are stimulating evidence-based policy formation. Planning towards a barrier-free society is another practical example of how the environment can be adapted to support health issues faced by urban residents. The World Health Organization's Healthy Cities initiative and its network, use a broad concept of health and provide concrete examples of how the negative aspects of urbanization can be overcome in the ongoing creation of health-supportive environments in the era of urbanization.

Key words Urbanization, Health promotion, Health-supportive environments, Healthy Cities, World Health Organization

Urbanization and Its Relation to the Health of the Population

According to UN statistics, as of the year 2000 three out of every four people in the industrialized nations live in cities.[1] Worldwide, about half of humanity, that is 2.9 billion out of the global population of 6.1 billion, presently lives in urban areas. The global population is projected to increase to more than 8.0 billion persons over the next 30 years. By that time the urban population will be 5.0 billion, therefore two-thirds of humanity will then be living in cities.[1]

Urbanization does not only pertain to major metropolitan areas such as Tokyo and New York. Taking Japan as an example, urbanization also affects the medium- and small-sized cities spread throughout every region of the country. In March 2004, Japan's urban population was 100,920,000, exceeding 100 million for the first time ever.[2] This figure equates to about 80% of the entire Japanese population, which means that four out of five Japanese now live in cities. Fifty years ago, during the 1950s, Japan's urban population was about half of what it is today. Japan's urban population is projected to continue growing on a relative basis, and to reach 85% of the total population in 2030.[2]

Many of the urban areas in Japan are smaller cities with populations of between 50,000 and 100,000, or mid-sized cities with populations of between 100,000 and 300,000. Urban lifestyles have become common in these smaller and mid-sized urban areas, as well as in big cities. Urbanization in such realms as food distribution, employment, and industry has come to influence the living environment of Japanese people in a

*1 Health Promotion, Division of Public Health, Graduate School of Tokyo Medical and Dental University; WHO Collaborating Centre for Healthy Cities and Urban Policy Research, Tokyo
Correspondence to: Takehito Takano MD, PhD, Health Promotion, Division of Public Health, Graduate School of Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Tel: 81-3-5803-5190, Fax: 81-3-3818-7176, E-mail: takano.hlth@tmd.ac.jp

great many regions across the country. Further, urbanization influences peoples' lives even outside of the urban areas. For example, no matter where you go in Japan today it is not all that difficult to locate convenience stores, supermarkets and fast food restaurants that are open 24 hours a day. The pre-made lunches that white-collar workers eat in central Tokyo were probably prepared in the middle of the night at food preparation plants located in the surrounding suburbs.

On the one hand, urban living, with its convenient environment, provides people with an abundance of lifestyle choices, some of which have positive and beneficial effects on human health. On the other hand, it is clear that urbanization has had a dramatic effect on many people's living environments and living conditions over the last 50 years, and that it is also responsible for numerous health problems.

Creation of Health-Supportive Environment: Healthy Japan 21

In 2000, the Japanese Ministry of Health, Labour and Welfare launched "Healthy Japan 21" as a new national health initiative for the 21st century.[3] Healthy Japan 21 differs greatly from prior national initiatives by emphasizing the importance of the environment in supporting human health.

Health promotion can often seem like an uphill struggle with the onus on individuals citizens to shoulder the burden of responsibility for their own health. Health promotion efforts to date have largely focused on equipping people with the requisite knowledge and skills to undertake this great feat, on the premise that it is up to individuals to protect their own well being.[4] However, many find the hill steep, the burden heavy, and the going too tough. By stressing self-responsibility to such an extent, there is a risk that some may grow tired of their task, stumble under the weight, and finish up worse, rather than better off.

In addition to providing knowledge and skills, Healthy Japan 21 also builds up an environment that supports health, making the uphill going easier. The other aspect of Healthy Japan 21 is that it secures the participation of local residents in the health promotion process; people to lend a hand along the way and share the load.

The health efforts made by individual citizens are important in boosting health levels and enhancing quality of life. At the same time, making provision in the environment to facilitate or support individual efforts is also extremely important. This approach is also recommended in the 1986 WHO Ottawa Charter for Health Promotion.[5]

Examples of the creation of a supportive environment for health include efforts towards prohibiting smoking and improving dietary habits. Japan's Health Promotion Law, which was drafted to advance Healthy Japan 21, requires measures to delineate smoking and non-smoking areas in public places. Furthermore, the prohibition of smoking and establishment of separate smoking areas has been put into effect in many public places including on streets and in train stations. There are also a growing number of enterprises that are working toward prohibiting smoking and establishing separate smoking areas. Such efforts provide valuable support for those struggling to succeed in quitting smoking.

Efforts to improve dietary habits include increasing the number of restaurants and cafeterias that provide healthy menus or menus which indicate the number of calories in each dish. A growing number of communities are also working to create environments that support healthy dietary lifestyles through educational efforts to improve nutritional habits among both adults and children.

Ensuring the availability of environments that encourage walking is also considered very important in promoting good health. If people can enjoy pleasant walks, if the locations and conditions for comfortable walking are all in place, then only minimal effort is required to effectively promote walking practices that lead to good health.

Four-stages of Medicine for Supporting Public Health: The McDermott Model

The evolutionary stages of medicine, a model proposed by McDermott that illustrates how human health needs to be supported, further contributes to an understanding of the relationship between humans and the environment in which they live.[6] Today, consideration of the creation of a health-supportive environment is based on McDermott's 4-stage model:

Stage I: As an initial foundation to support

human health, roads, bridges, dams, telecommunications systems and other infrastructural elements need to be put into place.

Stage II: The environment must be adapted for the provision of safe food and safe water. Efforts to improve the environment for the provision of clean air are also essential.

Stage III: Conditions for further advancing human health are established through the wide-ranging implementation of vaccination campaigns and other health promotion activities.

Stage IV: The provision of local medical services, based on good relations between doctors and patients, to support human health.

Taken together, these four stages promote health and function as an effective countermeasure to disease. The first two stages are fundamental and of particular importance.

The initial stage of preparing the infrastructure and the second of adapting the environment for the provision of safe food and water and clean air are directly linked to how well urban areas function.

Urban Green Spaces Contributing to Longevity of Senior Citizens

A study conducted in Tokyo revealed that urban environments rich in green areas, where the elderly can go for walks comfortably in the vicinity of their homes, begins to affect their health within five years.[7] The findings showed that those elderly who live in proximity to green areas and can safely go for walks without the passage of automobile traffic live 1.03 to 1.24 times longer than those who do not reside at such locations. These findings were based on a detailed five-year study of 3,144 individuals of 75 years and above.

It is of great interest to discover that such differences in daily living environments can give rise to differences in people's longevity, even in our highly-sophisticated contemporary society. The findings also underline the great importance of walking for the maintenance of health, as well as the importance of urban planning to facilitate walking.

Planning Towards a Barrier-free Society to Support Health of Local Residents

Another aspect being developed in Japan, is the creation of a barrier-free society, to facilitate walking by the elderly and by people with disabilities.

With the aging of society underway in Japan, the number of elderly who require nursing care is increasing. As people grow older, their physical balance often becomes less stable, and they can fall more easily. In many cases, after experiencing a fall or collapsing from illness the elderly need bed rest and ultimately require nursing care.

According to a survey implemented by the Ministry of Health, Labour and Welfare, one out of eight elderly Japanese comes to require nursing care as a result of such falls or collapses.[8] As a consequence, preventing the need for nursing care is gaining importance in the Japanese nursing care insurance system. This accounts for the growing popularity of "power rehabilitation" efforts to enhance the motor functions, muscle strength, and the elderly's sense of balance, and thus reduce the likelihood of falls and bone fractures that may accompany them.[9]

While it is naturally important to enhance the physical abilities of the elderly, it is also important to create urban areas where the elderly and individuals with disabilities can walk freely. Such efforts set off a virtuous cycle, which makes it possible for a great many people to walk in town without concern, which in turn upgrades the physical strength of the populace. In this manner, the creation of barrier-free urban areas, which adopt "universal-design" can provide areas where most people can live safely and healthily.

Japan's Ministry of Land, Infrastructure and Transport is presently advancing barrier-free urban development aimed at a society where individuals can move about freely and with peace of mind.[10] This largely concerns making trains, buses and other public transport, as well as local streets, barrier-free.

Local government bodies nationwide are establishing standards for barrier-free transportation, in accordance with Japan's Traffic Barrier-Free Law; and about 150 of them have already finished drafting their plans. These include, for example, the introduction of low-floor buses that are easier for the elderly to use, the construction of wide sidewalks that can accommodate wheelchairs, the elimination of cracks and level differences in pavements, the installation of elevators and escalators, and

securing space for wheelchairs in trains and buses, etc. The plans being drafted under the initiative of each local government body are bringing Japan closer to becoming a barrier-free society.

In essence, arranging urban areas where the elderly and individuals with disabilities can walk and live easily means creating spaces that are comfortable for everybody: both for ourselves and also for others.

These efforts to create barrier-free and universal-design towns and cities are sure to continue to advance from now on, centered around local residents and local government bodies. This type of urban planning supports the health of local residents, and should be viewed as an approach certain to upgrade the living environment.

Healthy Cities to Work on Developing Urban Infrastructure Supportive to Health

Advancing the health of the vast number of people who live in urban areas requires more than just individual endeavours. Efforts to upgrade the urban environment are also highly significant.

The WHO has been advocating the Healthy Cities Program as a comprehensive approach to improving urban environments.[11] This Program involves city-planning projects which create urban environments where people can live healthy lifestyles, which ensure safe and secure living environments, and implement this kind of urban development with the participation of the local residents.[12]

The WHO has been appealing to all cities in every country on earth to advance the Healthy Cities Program, and over a thousand cities worldwide are now participating in this initiative, including many in Japan.

Examination of multiple indicators of social determinants of health revealed associations of multiple factors on the health of the populations in cities and inter-relationships of those factors.[13] This evidence supports the Healthy Cities approach of engaging the participation of multiple sectors and government departments in the creation of health-supportive environments.

Cities are now facing global health problems including how to respond to emerging and re-emerging infectious diseases such as SARS and avian influenza. These issues cannot be thoroughly addressed by individual cities acting alone. To grasp the global influence of urbanization, to share information of its influence on human health, and to work together through sharing information of effective responses to these threats, cities themselves have formed a network aiming to work towards Healthy Cities.[14] Healthy Cities and its network is showing concrete examples of overcoming the negative points of urbanization and continuing to create health-supportive environments.

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Review Article

Laparoscopic Surgery and Cancer Metastasis

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Hideyuki Ishida*1

Abstract

Despite the wide spread use of laparoscopic techniques for malignant tumors, the oncological merits have not yet been fully determined. In this article, the author has reviewed reports of the therapeutic results of laparoscopically treated colorectal cancer and the literature for basic science experiments relating to CO_2 pneumoperitoneum and the mechanisms of spread and metastasis of cancers.

Since the introduction of laparoscopic surgery for colorectal cancer, port site metastasis has been noted as a phenomenon peculiar to laparoscopic surgery. Although the incidence of port site metastasis is decreasing with the technical advancement of laparoscopy, there are still problems that may not be solved with technology alone. Most of the currently reported results of prospective nonrandomized studies comparing laparoscopic and conventional colorectal resection did not show any difference in the prognosis of patients.

Numerous animal experiments have been undertaken to clarify the oncological effects of laparoscopic surgery, yet many have conflicting results. In order to evaluate the animal experiments related to laparoscopic surgery (pneumoperitoneum), this paper focuses on the duration and pressure of pneumoperitoneum as well as whether the clinical conditions are properly recreated.

This review of the literature concludes that the results of large scale prospective randomized controlled studies with carefully selected indications are necessary before laparoscopic surgery for malignant tumors such as colorectal cancer can be safely popularized.

Key words Laparoscopic surgery, Abdominal wall metastases, Hematogenous metastases, Colorectal cancer

Introduction

Laparoscopic surgery differs from conventional laparotomy in that it involves minimal access surgery performed through a small wound and in that it requires carbon dioxide gas to obtain a good operative field. The minimal invasiveness of laparoscopic surgery has been considered advantageous for oncological surgery, and has contributed to the increasing prevalence of laparoscopy for malignant tumors. However, a phenomenon peculiar to laparoscopic surgery, namely port site metastasis, has been widely noted by surgeons. Port site metastasis is a recurrent cancer occurring in the abdominal wall where the trocars for laparoscopic instruments and laparoscope are inserted. Recently, there have been increasing attempts to clarify the association between laparoscopic surgery and the spread of malignant processes.

In this article, the author reviews reports of the therapeutic results of laparoscopically treated colorectal cancer, which is the most common amongst malignant cases, and also reviews the literature on basic science experiments relating to CO_2 pneumoperitoneum and the mechanisms for the spread and metastasis of cancers.

*1 Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical School, Kawagoe
Correspondence to: Hideyuki Ishida MD, PhD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical School, 1981, Kamoda, Kawagoe, Saitama 350-8550, Japan.
Tel: 81-49-228-3700, Fax: 81-49-226-2229, E-mail: 05hishi@saitama-med.ac.jp, ishida@zb3.so-net.ne.jp
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Table 1 Incidence of port site metastasis

Study design	Number of cases (Number of reports)	Port site metastasis (%)
RCT	73 (2)	0 (0)
Registry	2,820 (5)	23 (0.82)
Prospective	829 (5)	3 (0.36)
Retrospective	1,472 (16)	11 (0.74)
Total	5,194 (28)	37 (0.71)

RCT: Randomized controlled study, Prospective: Prospective non-randomized

(The 10th EAES consensus meeting)

Table 2 Incidence of port site metastasis for different Dukes' stages (1993–1995)

	Dukes' stage	Months post op	First author	Reported year
1.	C	3	Alexander	1993
2.	B	10	O' Rou	1993
3.	C	6	Wals	1993
4.	C	10	Fusco	1993
5.	C	9	Cirocco	1994
6.	C	3	Nduka	1994
7.	B	6	Pasad	1994
	A	26		
8.	B	Not reported	Brends	1994
	C	Not reported		
	D	Not reported		
9.	A	9	Lauro	1994
10.	C	Not reported	Ramo	1994
	C	Not reported		
	C	Not reported		
11.	B	3	Cohen	1994
	B	6		
	C	6		
	C	9		
	C	12		
12.	B	10	Jacquet	1995
	B	9		
13.	B	2	Montorsi	1995

Laparoscopic Surgery for Colorectal Cancers

History

The first report of laparoscopic surgery for colon cancer was published in 1990 by Jacobs et al.[1] Their report included 7 cases of resectable colon cancer. Since then, there has been an increasing number of reports on laparoscopically treated colorectal cancers. Between 1994 and 2001, there were more than 15 publications reporting in excess of 200 cases of colorectal cancers treated by laparoscopy. In Japan, the indication of laparoscopic surgery was initially limited to early stage cancers, but recently, the inclusive criteria has grown to include advanced stages.

Port site metastasis

From Alexander et al.[2] report in 1993 up to 1998, there have been at least 168 case-reports of port site metastasis. There are several factors believed to be involved in port site metastasis, which forms a nodular tumor in the subperitoneal, muscular or subcutaneous layer at the trocar insertion site. (1) Due to immature operational skills, the cancer cells spread during surgery. (2) The isolated cancer cells adhere to the surgical instruments and implant in the abdominal wall when the instruments are repeatedly inserted and extracted. (3) The cancer cells become spread throughout the abdominal cavity as a result of the presence of carbon dioxide gas (aerolization) and either leak through the port or become implanted in the abdominal wall as the port is drawn out (chimney effect). (4) Pneumoperitoneum by carbon dioxide may have a positive effect on the implantation and growth of free cancer cells, or (5) it may stimulate hematogenous metastasis. Since the occurrence of port site metastasis clearly decreased with the increase of the experience of laparoscopic cases, the surgical technique is currently being called into question. At the consensus meeting of 10th EAES (European Association of Endoscopic Surgery) held in June 2002, 37 cases (0.71%) of port site metastasis were reported out of 5,194 cases of laparoscopic colorectal cancers (Table 1). Recently, the discussion of port site metastasis has been subsiding somewhat due to the recurrence rate at the surgical wound in conventional laparotomy being reported as 0.7–2.5% and because there may be a possibility of misdiagnosing recurrence at the abdominal wound in conventional open surgery. Although the incidence of port site metastasis is decreasing with the technical advancement of laparoscopy,

Table 3 Major non-randomized trial of laparoscopic surgery for colon cancer

First author	Year	Location	Compared to open laparotomy
Morris E	1996	Colon/Rectum	No significant difference in recurrence and survival
Leung KL	1997	Rectosigmoid	No significant difference in OS, DFS
Leung KL	1999	Right colon	No significant difference in OS, DFS
Lezoche E	2001	Colon	No significant difference in OS, DFS, local & hematogenous recurrence
Lezoche E	2002	Rectum	No significant difference in OS, DFS, local & hematogenous recurrence
Gerard G	2002	Colon/Rectum	No significant difference in recurrence and survival
Felicotti F	2002	Colon	No significant difference in DFS, local & hematogenous recurrence

OS: Overall survival, DFS: Disease free survival

there are still problems that may not be solved with technology alone. For example, port site metastasis occurs even in early stages (Dukes' A) and it is occasionally discovered early in the post-operative period (2–3 months) (Table 2).

Post-operative survival and type of recurrence

It is not possible to evaluate the safety and effectiveness of laparoscopic surgery for colorectal cancers without an objective comparison of conventional open surgery and laparoscopic surgery in terms of post-operative survival and type of recurrence. Large-scale prospective randomized controlled studies are currently underway in the United States of America, the United Kingdom, Australia, New Zealand, and other European countries. It will require at least another 3–4 years before the results of these long-term evaluations become evident. Most of the results of prospective nonrandomized studies comparing laparoscopic and conventional colorectal resection, which are currently available, show that the differences in overall survival, disease-free survival, the rates of local recurrence and hematogenous metastasis are negligible (Table 3).

Analyzing the Basic Science of Pneumoperitoneum and the Mechanisms of the Spread and Metastasis of Cancer

In order to evaluate the results of animal experiments related to laparoscopic surgery (pneumoperitoneum), the duration and pressure of pneumoperitoneum as well as whether the clinical conditions are properly recreated, have been investigated. The following summarizes major animal experiments involving laparoscopic surgery.

Pneumoperitoneum and biological defense

Pneumoperitoneum by carbon dioxide gas affects not only cancer cells but also immune system cells. Compared to open surgery, the activated T-cells and NK cells are thought to be better preserved in laparoscopic surgery, thus immunologically advantageous.[3] However, it is also known that the production of TNF (tumor necrosis factor) -α and IL (interleukin) -β by intra-abdominal macrophages decreases after carbon dioxide pneumoperitoneum.[4] Therefore, further detailed studies are required to clarify whether or not carbon dioxide pneumoperitoneum works in favor of immune related cells.

Experiments using cultured cancer cells

When using rat cultured colon cancer cells, Jacobi et al.[5] reported that carbon dioxide pneumoperitoneum promotes the growth of cancer cells, while helium gas suppresses the growth. Gutt et al.[6] reported the possibility that it is not only the use of carbon dioxide gas but also the extent of intra-abdominal pressure that is involved in the growth of cancer cells. The precise mechanism of cancer growth promotion by carbon dioxide pneumoperitoneum has not yet been clarified, and will require further investigation.

Subcutaneous transplantation of tumor

Allendorf et al.[7] performed a study comparing cancer growth in the subcutaneous tissue of a

Table 4 The effect of pneumoperitoneum on peritoneal dissemination

CO_2 pneumoperitoneum<Open laparotomy
Allendorf JDF (Arch Surg 1995)
Mathew G (Br J Surg 1996)
Bouvy ND (Br J Surg 1997)
CO_2 pneumoperitoneum=Open laparotomy
Hubens GH (Surg Endosc 1996)
Watson DJ (Arch Surg 1997)
Moreno EF (Surg Laparosc Endosc Percutan Tech 2000)
CO_2 pneumoperitoneum>Open laparotomy
Jacobi CA (Surg Endosc 1997)
Wittich P (Surg Endosc 2000): promoted more at 16 mmHg than 4 mmHg
Jacobi CA (Br J Surg 1998): promoted at 5 mmHg, 10 mmHg suppressed at 15 mmHg

Table 5 The effect of pneumoperitoneum on port site metastasis (animal model)

Abdominal lifting<CO_2 pneumoperitoneum
Nicole DB (Ann Surg 1996)
Bouvy ND (Ann Surg 1996)
Watson DI (Arch Surg 1997)
Neuhaus SJ (Br J Surg 1998)
Abdominal lifting=CO_2 pneumoperitoneum
Lecuru F (Surg Endosc 2002)
Abdominal lifting>CO_2 pneumoperitoneum
Agostini A (BJOG 2001)
He pneumoperitoneum<CO_2 pneumoperitoneum
Neuhaus SJ (Surgery 1998)
High pressure pneumoperitoneum<Low pressure pneumoperitoneum
Jacobi CA (Br J Surg 1998)
Canis M (Obstet Gynecol 1998): no difference between 4 mmHG and 10 mmHg

mouse transplanted with mouse breast cancer cells after surgical stimulation. They reported that open surgery clearly promoted the proliferation of cancer cells, while such an effect was much less pronounced in pneumoperitoneal surgery. Lee et al.[8] analyzed the PCNA (proliferating cell nuclear antigen) of the tumor in mice with mouse breast cancer cells transplanted to the subcutaneous tissue, and reported results concurring with those of Allendorf et al.[7]

Peritoneal dissemination

There have been numerous reports of experiments dealing with the effect on peritoneal dissemination. Most report that laparotomy promotes dissemination more than or at least equal to that of pneumoperitoneum, but there are some studies with contradicting results (Table 4). The timing of pneumoperitoneum in relation to the transplant of tumor cells, the intra-abdominal pressures, the types of gas, the duration of pneumoperitoneum, the species, the types of transplanted cells, etc. must be identified and investigated as independent variables for making integrated decisions.

Table 6 The effect of pneumoperitoneum on hematogenous metastasis

Liver Metastasis
CO_2 pneumoperitoneum>Open laparotomy
Ishida H (Surg Endosc 2002): rabbit, portal transplant of VX_2 cells
CO_2 pneumoperitoneum>Open laparotomy, abdominal lifting
Gutt CN (Surgery 2000): rat, portal transplant of colon cancer cells
Ishida H (Surg Endosc 2002): mouse, portal transplant of colon cancer cells
Gutt CN (Br J Surg 2001): rat, portal transplant of colon cancer cells, hepatic micrometastasis formed
CO_2 pneumoperitoneum = Open laparotomy
Ishida H (World J Surg 2001): rabbit, portal transplant of VX_2 cells, hepatic micrometastasis formed
Tomita H (Dis Colon Rectum): rat, portal transplant of colon cancer cells
Ishida H (Surg Endosc 2002): pneumoperitoneal pressure↑ leading to liver metastasis↑, mouse, portal transplant of colon cancer cells
Lung Metastasis
CO_2 pneumoperitoneum = Open laparotomy
Tomita H (Dis Colon Rectum): rat, portal transplant of colon cancer cells
CO_2 pneumoperitoneum<Open laparotomy
Shiromizu A (Surgery): mouse, portal transplant of colon cancer cells
Ishida H (Surg Endosc 2000): pneumoperitoneal pressure↑ leading to lung metastasis↑, mouse, transplant of colon cancer cells via tail vein

Port site metastasis

The incidence of port site metastasis is more often reported in pneumoperitoneum than in abdominal lifting. Some reports suggest that the incidence is equal and others even contradict the more common results, stating that the incidence is higher in the abdominal lifting method. There are reports of a lower incidence in helium pneumoperitoneum than in carbon dioxide pneumoperitoneum and also of a lower incidence in low pneumoperitoneal pressure as compared to high pneumoperitoneal pressure, but some reports suggest that there is no relation to the level of pneumoperitoneal pressure (Table 5). Reports of experiments dealing with the site of trocar insertion in addition to the investigation of intra-abdominal environment and port site metastasis are sparse. In our recent study[9] using port site metastasis model with rabbit VX_2 cancer cell line, the results suggested that the local factors of trocar placement such as ischemia and crush injury are more important than pneumoperitoneum itself.

Hematogenous metastasis

Table 6 shows animal experiments investigating liver and lung metastases. In our study[10] using liver metastasis model with rabbit VX_2 cancer cell line, the results showed that the incidence of liver metastasis is higher in 45 mm open laparotomy as compared to 10–12 mmHg pneumoperitoneum. Almost at the same time, Gutt et al.[11] reported that gasless laparoscopy resulted in less liver metastasis than in carbon dioxide pneumoperitoneum using the rat liver metastasis model. Using colon 26 cells in the mouse liver metastasis model, we showed that intra-abdominal pressure rather than duration of pneumoperitoneal appears to be the promoting factor of liver metastasis in carbon dioxide pneumoperitoneum.[12] Furthermore, by labeling the colon 26 cells with ^{111}indium oxine, we clarified that with rising intra-abdominal pressure, the cancer cells transplanted into the portal system tend to accumulate in the liver.[12]

In regards to lung metastasis, there have not been any reports indicating that pneumoperitoneum promotes metastasis to a greater extent

than open surgery. Similar to liver metastasis, we found that the incidence of lung metastasis increases with greater intra-abdominal pressures. The promotion of hematogenous metastasis with increasing intra-abdominal pressure is thought to be associated with a decrease in intra-organ blood perfusion caused by high intra-abdominal pressure. However, there may be other factors that require further investigation. In experimental models in which cancer cells have already passed the implantation period and formed micrometastasis, or models with cancer cells orthotopically transplanted to the bowel wall (thought to be closer to clinical picture), there are scant reports of differences in hematogenous metastasis between open laparotomy and pneumoperitoneum.

Conclusion

To ensure the safe popularization of laparoscopic surgery for malignant tumors, it is important to wait for the results of large scale prospective randomized controlled studies and to select the indications carefully. Even if the results indicate that there is no difference in long-term outcome between conventional open surgery and laparoscopic surgery, it is still important for the surgeons to understand the mechanisms and potential risks of the effects of laparoscopic surgery (pneumoperitoneum) on the spread and metastasis of malignant disease.

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Simultaneous Hepatitis E and Paratyphoid Fever

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Kenji Ohnishi,[*1] Yasuyuki Kato,[*1] Nobuhiro Komiya,[*1] Kayoko Hayakawa[*1]

Abstract

We recently treated a Japanese man who, upon his return from India, presented with a co-infection of the hepatitis E virus (HEV) and *Salmonella* Paratyphi A. Our experience with this patient underlined the importance of investigating HEV-RNA and antibodies against HEV in patients recently returned from tropical or subtropical areas who manifest elevated serum aminotransferase levels, even when they are infected with other infectious diseases.

Key words Hepatitis E virus, *Salmonella* Paratyphi A, India

Introduction

Hepatitis E caused by infection with the hepatitis E virus (HEV) and paratyphoid fever caused by *Salmonella* Paratyphi A (*S.* Paratyphi A) are endemic in tropical and subtropical areas. However, to our knowledge, only 2 cases of the co-existence of these two conditions have been reported in the literature.[1,2] We recently treated a Japanese patient who, upon his return from India, presented with hepatitis E complicated with paratyphoid fever. After recounting the details of this patient co-infected with HEV and *S.* Paratyphi A, this paper discusses the importance of screening for hepatitis E in sickly patients returned from HEV endemic areas even when they are infected with other infectious diseases.

Case Report

A 24-year-old Japanese man traveled in India for 2 months and returned to Japan on August 26, 2003. He visited another hospital on September 13 because of 2 days of fever. In the past, his health had been unremarkable. *S.* Paratyphi A was cultured in his blood and stool, and he was diagnosed as having paratyphoid fever. Upon his admission to our hospital by referral on September 22, 2003, his only definite abnormality on physical examination was a fever of 39.4°C. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin (T-Bil), and C-reactive protein (CRP) were 116 IU/l, 100 IU/l, 867 IU/l, 375 IU/l, 1.1 mg/dl, and 6.13 mg/dl, respectively. The *S.* Paratyphi A isolated from the patient was resistant to ofloxacin, so he was treated with cefotaxime from September 22 to October 5. Immunoglobulin G (IgG) class antibodies to cytomegalovirus (CMV) and the Epstein-Barr virus (EBV) were detected, but the patient tested negative for immunoglobulin M (IgM) class antibodies to these viruses. The patient's hepatitis A, B, and C serology was negative. Ultrasonography revealed no stones in the gall bladder or the bile duct. The patient was defervescent on September 29 and discharged on October 6. The serum laboratory data on October 6 were as follows: AST 56 IU/l, ALT 116 IU/l, LDH 221 IU/l, ALP 424 IU/l, T-Bil 0.7 mg/dl, and CRP 0.19 mg/dl.

Three weeks later, on October 27, 2003, he was readmitted to our hospital because of 4 days of fever and identification of *S.* Paratyphi A in his

*1 Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, Tokyo
Correspondence to: Kenji Ohnishi MD, Department of Infectious Diseases, Tokyo Metropolitan Bokutoh General Hospital, 4-23-15 Kohtohbashi, Sumida-ku, Tokyo 130-8575, Japan. Tel: 81-3-3633-6151, Fax: 81-3-3633-6173, E-mail: infection@bokutoh-hp.metro.tokyo.jp

Table 1 Serum AST, ALT, LDH, and T-Bil concentrations (in 2003)

	Sep. 22	29	Oct. 6	27	Nov. 7	11	13	17	19	25	Dec. 4	18
AST (IU/l)	116	207	56	146	155	357	697	3,545	3,908	254	ND	ND
ALT (IU/l)	100	219	116	148	208	363	588	1,949	2,405	665	139	66
LDH (IU/l)	867	441	221	487	377	280	331	863	533	212	ND	ND
T-Bil (mg/dl)	1.1	0.7	0.7	3.5	1.4	2.8	4.3	8.9	12.3	6.3	3.1	1.6

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, ND: not done

stool and blood. His body temperature was 38.3°C on admittance. The laboratory data on October 27 were as follows: AST 146 IU/l, ALT 148 IU/l, LDH 487 IU/l, ALP 469 IU/l, T-Bil 3.5 mg/dl, and CRP 6.46 mg/dl. He was diagnosed as having relapsed paratyphoid fever and was treated with azithromycin from October 27 to October 30, and then ceftriaxone from October 30 to November 8. His body temperature was 39.9°C on October 29, but he was defervescent on November 5. His serum concentrations on November 7 were as follows: AST 155 IU/l, ALT 208 IU/l, LDH 377 IU/l, ALP 1,369 IU/l, T-Bil 1.4 mg/dl, and CRP 0.59 mg/dl, and he was discharged on November 8, 2003.

Five days later, on November 13, 2003, he was readmitted to our hospital when the following data were obtained at our outpatient clinic: AST 697 IU/l, ALT 588 IU/l, LDH 331 IU/l, ALP 1,473 IU/l, T-Bil 4.3 mg/dl, and CRP 0.59 mg/dl. However, the patient did not complain of fever. His continuous stool cultures revealed no *S.* Paratyphi A while in this admission. The laboratory data on November 19 were as follows: prothrombin time 77.5%, AST 3,908 IU/l, ALT 2,405 IU/l, and T-Bil 12.3 mg/dl, and treatment with glucagon insulin therapy was initiated. PCR revealed HEV-RNA (genotype 1) in his serum obtained on October 27, but not in his serum obtained on November 16, and HEV-IgG antibody was identified in his serum collected on both October 27 and November 16. On these bases, he was diagnosed as having hepatitis E. The HEV-RNA, HEV-IgG antibody tests were performed at the Tokyo Metropolitan Institute of Public Health. The patient recovered and was discharged on November 29. The serum levels of AST, ALT, LDH, and T-Bil are shown in Table 1.

Discussion

The incubation period of paratyphoid fever ranges from 1 to 3 weeks, while that of hepatitis E ranges from 2 to 10 weeks.[3] Our patient was therefore likely to have been infected with these causative organisms in India, where both diseases are endemic. The genotype of HEV isolated from domestically infected patients has been reported to be type 3 or 4 in Japan.[4,5] In our patient, the genotype of HEV was type 1, a very common genotype in India.[6] This confirmed that he was likely to have been infected with HEV in India.

Mildly elevated levels of serum AST, ALT, LDH, ALP, and T-Bil are commonly observed with typhoid fever and paratyphoid fever, but these abnormalities are generally improved in patients with good therapeutic effect. If elevated serum levels of AST, ALT, LDH, ALP, and T-Bil persist in patients returned from tropical and subtropical areas and they have no serological markers of ongoing infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, or EBV, the presence of HEV-RNA or antibody against HEV should be investigated.

In a single volunteer study of HEV transmission, HEV was reported to become positive in stool at the onset of the icteric phase and to remain positive until the ALT activity peaked.[7] In contrast to HBV and HCV, the mode of transmission of both HEV and HAV is fecal-oral. While hepatitis E has an overall mortality rate of only 0.07–0.6%, it can be particularly severe among pregnant women, with mortality rates reaching as high as 25%.[3] The prompt identification of patients with acute hepatitis E and timely and thorough measures to prevent contact

transmission from these patients to others are essential within a hospital. This paper emphasizes the importance of screening for hepatitis E in patients who, upon returning from tropical or subtropical areas, manifest high levels of serum aminotransferase, regardless of whether they suffer from other infectious diseases.

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Problems in Medical Care Services for Children

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Toshiaki Hakui*1

Key words Pediatric medicine, Emergency care, Preventive vaccination, Child rearing, Decreasing birth rate, Medical fee

Introduction

With progress in pediatric medicine and the medical care of children, the infant mortality rate in Japan has become the lowest among the Group of Seven industrialized nations. However, the medical care of children is a monetary drain on Japan's medical insurance system, and much remains to be improved in terms of hardware and systems of allocating subsidies, among others, in the areas of emergency care, hospitalization, preventive vaccination, and support for child rearing. Some of these problems in the medical care of children in Japan are discussed below. In particular, shortages of pediatricians and obstetricians and gynecologists are an issue of urgent concern.

Number of Pediatricians

First, the number of pediatricians is an important concern. The overall number of doctors increased from 220,853 in 1994, when statistical data first became available, to 249,574 in 2002, showing an increase of about 30,000 individuals. In contrast, the number of doctors with a major specialty in pediatrics increased by only about 1,000, from 13,346 to 14,481, during the same period. These pediatricians account for only 6% of all doctors. Further, half of all pediatricians working in clinics are over 60 years of age. The number of internists or other medical specialists who have pediatrics as a minor specialty is also decreasing annually because of the aging of doctors, resulting in a decreased number of clinics that care for diseased children. These statistics indicate that increasing the number of pediatricians and pediatric clinics is an issue of urgent concern for the future.

Economic Aspects of Pediatric Medical Services

In Japan, increases in reimbursements for medical fees have tended to be lower in the pediatric field than in other areas of medical practice. This constitutes one of the reasons for the economic problems that beset pediatric medical services. Although medical fee per case has increased steadily in recent years, the overall revenue of pediatric clinics has not increased because of the declining number of patients resulting from a decrease in the pediatric population and concomitant decrease in severe illnesses. In addition, unlike other medical fields, medical services in the area of pediatric medicine depend in large part on the physician's skills, which are not tangible and cannot be incorporated into fees for specific treatments. Tests and procedures designated for remuneration are fewer than in other medical fields, and this also contributes to the economic difficulties of pediatric medical practice.

Among the national costs of medical care reported by the Japanese Ministry of Health, Labour and Welfare, medical expenses in the category of general practice for people aged 60

*1 Japan Medical Association, Tokyo
Correspondence to: Toshiaki Hakui MD, Japan Medical Association, 2-28-16, Honkomagome, Bunkyo-ku, Tokyo 113-8621, Japan.
Tel: 81-3-3946-2121, Fax: 81-3-3946-6295, E-mail: jmaintl@po.med.or.jp

years or older account for more than 60% of total inpatient care expenses and more than 50% of total outpatient care expenses, whereas medical expenses for children under 15 years of age account for only about 4% of total inpatient care expenses and about 9% of total outpatient care expenses. This issue deserves further discussion, considering the fact that there is no great difference between the overall numbers of elderly patients and pediatric patients.

In pediatric medical practice, special assistance from staff is necessary because most young children cannot remove their clothing by themselves before an examination or extend their own arms for blood collection. Therefore, the pediatric department requires that a number of nurses or other medical assistants be employed. As a result, pediatric clinics incur more personnel expenses than those in other fields of medicine, and are thus more likely to encounter financial difficulties.

According to the Ministry of Health, Labour and Welfare, there has been little change since 1993 in the percentage of inpatients aged 1–14 years among total inpatients, whereas the corresponding percentage of inpatients within 1 year after birth has been decreasing markedly since its peak in 1997.

On the other hand, the percentage of outpatients aged 0–14 years among total outpatients in 2002 was markedly decreased in comparison with that in 1993. The major underlying factor seems to be a distinct decrease in the population of children owing to the continuing decline in births in Japan. The birthrate has been decreasing since 1960, and the child population has been declining since 1982. In contrast, the number of the elderly aged 65 years or older has been increasing since 1947. Therefore, the percentage of children aged 0–14 years in the total population is now 15%, similar to that of those aged 65 years or older. The percentage of elderly is, however, increasing, leading to a progressive decline in the percentage of children and to aging of the overall population. This trend continues despite various countermeasures that have been attempted.

Both in- and outpatient care of children must attempt to relieve the physical and mental suffering of the patients and their families, and thus requires continuity of proper care. In addition, the possibility of substantial stress occurring from hospital admission should be minimized through careful consideration and attention. Another factor is that, even in hospital, children require amusements and recreation suitable for their age and condition and may need school education as well. Therefore, the pediatric department of a hospital requires a great deal of labor for both medical and non-medical activities, including assistance in eating, putting on and taking off of clothes, changing diapers, etc. The examination and treatment of children require more personnel than in the case of adults. Assistance from two or more medical personnel may be needed, and anesthesia may be required for the examination.

The pediatric division also requires isolated rooms for children with infectious diseases, and playrooms are necessary for children in the convalescent stage. Thus, in contrast with adults, the medical care of children requires more funding for hardware and personnel and more time for examination and treatment. In addition, sufficient nighttime staff, including doctors and nurses, is indispensable to enable infants who cry during the night to return to sleep calmly and to deal with pediatric patients who are admitted to the hospital at night. The surcharge for infant care prescribed for remuneration under the medical insurance system does not provide for the actual expenditures of the division. It is also necessary to always keep some beds available to prepare for unexpected admissions, as in the emergency care division. Recently, several hospitals have closed their pediatric divisions. The two main reasons for closure were (1) failure to overcome the deficit caused by hardware expenditures and (2) shortage of pediatricians.

The burden imposed on hospital pediatricians who must cope with this pressing situation continues to increase, while the number of young doctors entering the field of pediatrics is decreasing. This situation contributes to an increased workload for practicing pediatricians and creates a viscous cycle that leads to worsening of the shortage of pediatricians.

In addition to these problems, formulation of a proper system for pediatric emergency care is an urgent issue. Although an emergency care center should provide the main support for patients in serious condition, the equipment in pediatric intensive care units of emergency care centers is worse in quantity and quality than that of intensive care units for adult patients nationwide.

In the future, it will be necessary to devise a system by which doctors specializing in pediatric medicine provide care as a skilled pediatric team within a division specializing in the medical care of children.

Pediatric Emergency Care

Pediatric emergency care particularly on holidays and at night is provided in various forms by holiday and nighttime emergency clinics managed by the Japan Medical Association, emergency outpatient clinics in hospitals, and emergency centers managed jointly by the local government and local medical association. However, resources for pediatric emergency care, i.e., the number of pediatricians available, distribution of facilities and hospitals that can provide emergency care, and subsidies, vary widely among different localities, and there is a large gap between the existing situation and people's desire for high-quality care provided by pediatric specialists regardless of where the patient lives. As a result, pediatricians are driven to overwork, leading to a breakdown of the current system of pediatric emergency care. Pediatricians working in clinics also spend a considerable amount of time outside office hours working as emergency care providers on call or at emergency care centers outside their offices. However, in recent years, the number of doctors living outside the clinic has been increasing, another reason why medical care outside office hours is difficult to provide.

Thus, the provision of pediatric emergency care involves complicated problems that originate from differences in hardware among different localities, shortages of pediatricians, and patient demands that medical care be available anytime, anywhere, almost like a 24-hour convenience store.

In the future, in addition to the enhancement of intensive care units specializing in pediatric treatment, the Japan Pediatric Society's plan should be promoted aggressively. This plan centers on base hospitals and pediatric emergency telephone consultation services that are being initiated in various places in the country. It is important to attempt somehow to make good use of the limited number of pediatricians in order to realize progress in pediatric emergency services.

Preventive Vaccination

Another issue of concern in the area of pediatric medical care is that of preventive vaccination. To increase the efficacy of preventive vaccination, a promising means of preventing infectious diseases, it is important that the vaccination rate be increased. In order to develop a system of safe vaccination by increasing the vaccination rate and minimizing adverse effects, the traditional form of public "mass vaccination" was changed to "individual vaccination."

In cases of "individual vaccination," it is necessary that vaccination be performed by a family doctor who is familiar with the normal health condition of the vaccinee and can communicate easily with the vaccinee and his/her parents, thereby avoiding vaccination of ineligible children and health problems attributable to vaccination. However, because the family doctor may not live in the same municipality as the vaccinee, the system needs to allow children to receive preventive vaccinations beyond the boundaries of their particular municipality. In other words, a system of extended preventive vaccination is desirable. More specifically, with the cooperation of medical groups such as local medical associations, each municipality would entrust vaccination to medical facilities in other areas to allow residents to undergo preventive vaccination beyond the boundaries of the administrative district within the same prefecture.

Unfortunately, extended vaccination services on a prefectural basis are not yet available throughout the country, and extended vaccination services are not yet satisfactory even in relatively large cities like government-designated major cities and cities with public health centers.

Extended preventive vaccination services that allow vaccination by family doctors anywhere within the same prefecture is a matter of urgent necessity in order to increase the vaccination rate and efficacy of vaccination and to promote the implementation of safe vaccination.

Support for Child Rearing

Another important issue related to pediatric medical services is support for child rearing. Current medical subsidies for infants and young children provide support for medical expenses.

These programs, begun in 1973 and employing public funds, cover a portion of the medical expenses the patient pays to the medical institution. Although such programs are available in 3,241 municipalities, program content varies widely according to the sponsoring municipality. For example, these subsidy programs are applied to children up to 6 years of age, or preschool children, in about half of the municipalities, whereas one-third of the municipalities limit their programs to infants 2 years of age or younger. In addition, about two-thirds of the municipalities provide programs without regard to income, and benefits in kind are provided in about half the municipalities. Thus, the subsidy is provided in different ways and with different requirements according to the dictates of the local government.

However, the fact that there are large differences in the treatment of children according to their place of residence is an important issue in view of their right to equal medical care as provided in the context of the right to life in Article 26 of Japan's constitution. When the age limit of the medical expense subsidy for infants and young children is low, the percentage of children treated in outpatient or inpatient clinics is also low. It seems necessary to standardize the methods and requirements of the subsidy.

As a specific support for child rearing, a program provides temporary nursing for health support, which is a day care service for children who are sick or who have just gotten over a disease. Governmental support programs for child rearing are not only part of the policy of support for working parents but are also included in the support project for child rearing in the community as a means to prevent the decline in fertility, based on an action plan under the Measures to Support the Development of the Next Generation. These programs are designed to promote the enhancement of various childcare services. However, these programs have not been sufficiently effective in each district to meet the current needs for childcare support. Under the current form of care for sick/convalescent children, care centers annexed to medical facilities have increased in number. These care centers are useful because they can assist children in the acute stage as well as in the convalescent stage of disease. At the same time, however, they are burdened by burgeoning expenses for personnel and high initial costs. On the other hand, management of day-care centers and infant homes requires close cooperation with family doctors, local medical institutions, and doctors of the nursery facilities, and various problems remain to be solved.

In order to avoid worsening of the current shortage of pediatricians, it is necessary to make good use of their manpower. In addition, further improvement of subsidies from administrative organs and remuneration for pediatric medical care, as well as the system of support for child rearing, will be particularly important.

Like hospitalization, the purpose of sick/convalescent childcare is not simply to assume the care of children in lieu of their parents when the child is ill. Another significant purpose is to provide total care of the child through the involvement of experts in various fields, thereby meeting the physical, mental, socioeconomic, and educational needs of the child. In this respect, the role of pediatricians is extremely important, beginning with the management of the system and risk management, in addition to economic issues and health control. Thus, further discussion is desirable.

Anxiety over Child Rearing

Finally, the issue of the response of pediatricians to parental anxiety over child rearing will be considered. The nuclear family has become common in Japanese society, and, when the younger generations who have grown up under this particular family structure become parents, they may have to rear their children in the absence of a large extended family that can provide help and advice. It is important during regular public checkups of babies and infants and in daily clinical practice to provide appropriate information to such parents, to lessen their anxieties about childrearing. Enough time should be spent to listen to their concerns and to speak with them kindly and comprehensively.

Children's diseases include many conditions characterized by abrupt onset and high fatality, such as acute fever and related febrile seizure, gastrointestinal disease-derived diarrhea, vomiting, and subsequent dehydration, and respiratory disorder. Characteristically, urgent actions are required because of rapid disease progression. To lessen parents' anxiety about such diseases, emergency telephone consultation and holiday and

nighttime emergency care services seem to be helpful. In addition, pediatricians should not only provide adequate information about children's diseases, but also be positive in giving advice about child rearing, to address parents' anxiety.

Although there is increasing demand for children's diseases to be treated by pediatric specialists, pediatricians currently have to spend a great deal of time outside their daily clinical practice in public affairs such as health checkups of babies and infants, preventive vaccination, and duties as entrusted doctors for schools, kindergartens, and day-care centers.

In the field of pediatric medical care, it is necessary to address preventive medicine and medical care to improve the health of diseased children, through the use of current manpower, even though it may be insufficient.

Conclusion

In summary, problems related to providing pediatric medical care include the small increase in the number of pediatricians relative to the total increase in the number of doctors. In addition, pediatricians working in clinics are decreasing owing to the aging of many clinic pediatricians. On the other hand, people's demand for pediatric specialists is particularly strong in comparison with other specialties. Although the mobilization of pediatricians for holiday and nighttime emergency care has been intensified, their efforts have not been duly appreciated in light of the relatively severe working environment and the fact that the department of pediatrics is often a financial drain on the hospital. Further, given the current circumstances, those practicing in pediatric clinics are generally pressed for time. There is an urgent need for these problems to be solved to make pediatric medical care more appealing and to ensure that more young pediatricians are available for the next generation.

In regard to the current losses in revenue being sustained by pediatric medical services, as long as children continue to be dealt with merely as small adults in the calculation of medical fees under the current health insurance treatment system, the management of pediatric departments and clinics seems problematic. People tend to expect 24-hour medical services from pediatricians to be available near their homes. To fulfill these expectations, an increase in pediatricians, more home doctors, maintenance and reinforcement of facilities, and financial backup from the national government are indispensable.

With regard to parental anxieties about child rearing, it would be helpful to have pediatricians be the point of entry into the local government system in order to ameliorate parents' worries, in addition to solving the various health problems of their patients. Pediatricians have the advantage that not only the patient but also the patient's mother, father, and even grandmother and grandfather may be available for consultation. Because people tend to expect that children be raised to healthy, contributing members of society, it is important to resolve issues in pediatric medical care to establish a medical environment that allows for the healthy growth of children. Now would be the time to build a medical care system specific to the needs of children.

Children are the nation's treasure. In order to promote the healthy growth of children who will support the future of the country, enactment of a new law specific to pediatric affairs involving the reimbursement of medical fees, emergency care, preventive vaccination, and support for child care is desirable. To ensure that every child has equal access to safe, high-quality medical care at any time or place, the government needs to address these issues aggressively to actualize enhanced medical care services for children. This will enable the children of the 21st century to grow up to lead a happy and healthy life.

Guidelines for the Treatment of Gastric Cancer

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Yosuke Adachi*1

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Characteristics of Gastric Cancer

Gastric cancer has three characteristics. Firstly, it is a very common disease. Even today gastric cancer is one of the most prevalent cancers and is responsible for amongst the highest number of deaths. Because gastric cancer is a widespread disease, medical practitioners need to have good knowledge of this disease to practice medicine in daily clinical activities.

Secondly, gastric cancer has different stages. Some gastric cancers have the form of either an early cancer treatable by physicians without surgery or an advanced cancer for which even surgical intervention is ineffective. In the majority of cases, the cancer is diagnosed at an early stage, yet the annual number of deaths is around 50,000.

Thirdly, histologically, gastric cancer can be divided into two types: a well-differentiated type and a poorly-differentiated type. Histologic type is an important indicator of disease progression and patient prognosis, and, therefore, is essential for the treatment of gastric cancer.[1]

History of Treatment of Gastric Cancer

The treatment of gastric cancer began with the gastrectomy for gastric cancer successfully performed by T. Billroth in 1881. Japan has long been a world leader in the treatment of gastric cancer, with developments such as the extended lymph node dissection developed by T. Kajitani, the gastrocamera developed by T. Uji and the double-contrast technique developed by H. Shirakabe.

1962 saw the establishment of the Japanese Research Society for Gastric Cancer which issued the General Rules for the Gastric Cancer Study, and thus created a forum in which doctors could discuss the diagnosis and treatment of gastric cancer using the same standards to compare treatment outcomes throughout Japan.[2]

In 1997 the Japanese Gastric Cancer Association was established, publishing its Gastric Cancer Treatment Guidelines four years later in 2001. These were the first guidelines on the treatment of cancers in Japan, and consisted of separate guidelines for doctors' use and guidelines for general use, and in 2004 a revised edition was published.

Guidelines for the Treatment of Gastric Cancer

Events leading up to the creation of the current set of guidelines for doctors and the Japanese public have been described above. The 2004 guidelines include recommendations on up-to-date treatment techniques for different stages of gastric cancer.

The following text describes the rationale behind the creation of these guidelines, namely: 1) to identify the proper indications for the treatment of gastric cancer, 2) to minimize the

*1 Department of Oncologic Surgery, Gifu University, Gifu
Correspondence to: Yosuke Adachi MD, Department of Oncologic Surgery, Gifu University, 1-1 Yanagido, Gifu 501-1194, Japan.
Tel: 81-58-230-6230, Fax: 81-58-230-6236, E-mail: adachi@cc.gifu-u.ac.jp

difference between centers, 3) to seek to improve safety and treatment outcomes, 4) to eliminate unnecessary treatment, and 5) to facilitate mutual understanding between doctors and patients.

The guidelines are based on the principle of selecting the right treatment according to stage. Informed consent is important for the selection of treatment, and doctors have a responsibility to explain the available treatment options and various stages of treatment to patients.

Treatment Modalities According to Stage of Gastric Cancer

The stage of gastric cancer is determined by the depth of wall invasion and the status of lymph node metastasis. The depth of wall invasion can be assessed fairly accurately by means such as barium meal study, endoscopy and endoscopic ultrasound, but as clinical measurement and clinical assessment of the status of lymph node metastasis are inaccurate, treatment is determined mainly on the depth of wall invasion.

Although there are exceptions, early cancer, in which invasion is restricted to the mucosa or the submucosa, can be managed by endoscopic treatment or limited surgery. However, ordinary cancer that invades the muscular layer, the subserosal layer and the serosa can be treated using standard surgery, while advanced cancer that invades the surrounding organs requires extensive surgery.

Standard surgery is defined here as distal gastrectomy i.e. resection of two thirds or more of the stomach, or total gastrectomy, together with D_2 lymph node dissection. Limited surgery is also known as function preserving surgery and includes pylorus-preserving gastrectomy, proximal gastrectomy, segmental gastrectomy and partial gastrectomy.

Endoscopic Treatment

With endoscopic treatment, note the standards for application and residual recurrence. Endoscopic treatment is limited to mucosal cancer, and is applied to well circumscribed, well differentiated type cancers of up to 2 cm in size. Recently large lesions can also be resected using an insulated-tip knife.

Data for 3,000 people who underwent endoscopic treatment at typical centers in Japan showed that the frequency of residual recurrence following endoscopic treatment is 12%, and that the period until recurrence varies. Consequently, regular endoscopic examinations are recommended following this treatment.[3]

Laparoscopic Surgery

Even though laparoscopic surgery on gallstones offers advantages including reduced pain, faster recovery, shorter hospital stay and earlier return to social activity, laparoscopic surgery for gastric cancer is currently still regarded as a technique performed for research purposes at some centers and is not recognized as a routine treatment technique.

S. Kitano of Oita University was one of the first in the world to perform laporoscopic surgery for gastric cancer. Alongside animal experiments and basic research, he carried out case studies, case-control studies and clinical trials, verified his own surgical outcomes in terms of both safety and efficacy, and reported the data to overseas journals.[4–7]

Reach of the Guidelines

Guidelines are not legally binding, are for guidance purposes only, and may be followed at the doctor's discretion. The binding force of guidelines against decision-making of clinical behavior is the same or not stronger than that of recommendation.

Anything that is applicable to 95% or more of patients in clinical practice is considered a standard. The percentage of patients covered by the guidelines is around 60–95%.

The guidelines are based on evidence and may assist decision-making by doctors and patients. Guidelines are intended to prevent potentially self-righteous clinical behavior.

Clarification of Routine Diagnosis and Treatment

The guidelines are based on the results of pathological diagnosis of resected specimens. It is important to continue to accumulate data based on clinical diagnosis during the course of treatment of gastric cancer in order to reduce the risks of intervention for patients and to make

further advances in treatment techniques.

Methods such as endoscopy and laparoscopy are being actively introduced to the treatment of gastric cancer. It is important not only to analyze potential short-term complications resulting from such new treatment techniques, but also to assess the long-term safety and efficacy including recurrence rate, survival rate and quality of life (QOL).

In decision-making for routine diagnosis and treatment, it is necessary to consider three factors, namely the doctor's opinion, the patient's opinion and the evidence. From the view point of clinical ethics, it is also necessary to ensure there is an ethical basis for clinical intervention. To this end consideration of medical indications, QOL, patient references, and contextual features is required.

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