P-01

# Bibilometric study of meta-analysis literatures, 1990-2003

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**Objective:** Research activities using meta-analisis are vigorous in clinical fields. We surveyed recent meta-analysis literatures from the view of bibilomertic study.
**Methods:** We searched MEDLINE database (1990 through 2003) using PubMed publication type tag, meta-analysis. We retrieved 8,679 meta-analysis literatures. Those literatures analyzed by publication year and research topics. Research topics classified by the Medical Subject Headings categories produced by US National Library of Medicine.
**Results:** Meta-analysis literatures produced 274 articles in 1990, 427 in 1995, 846 in 2000, and 1258 in 2003. These figures shows that meta-analyses are certainly growing. Research topics of meta-analysis are disease oriented, 28.5%, chemical and drugs, 17.9%, diagnosis and therapeutic techniques, 14.2%, and biological sciences, 10.7%. In diseases category, primary topics are neoplasms, secondary, cardiovascular diseases, and tertiary, nervous system diseases.
**Conclusions:** Meta-analysis literatures are growing year by year from 1990 through 2003. Main research topics are diseases, and drugs.

P-02

# Comparison of cilostazol and ticlopidine coadministered with aspirin for long-term efficacy and safety after coronary stenting; A meta-analysis

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**Purposes:** To compare cilostazol with ticlopidine for efficacy and safety as an adjunctive antiplatelet therapy after coronary stenting.

**Methods:** Published clinical studies retrieved through Medline and other databases from 1981-2004. Meta-analyses evaluated efficacy and adverse clinical events for cilostazol or ticlopidine coadministered with aspirin after coronary stenting. Major adverse cardiac events (MACE), quantitative coronary angiographic parameters (QCA) including minimal lumen diameter (MLD), late loss, loss index of diseased vessels, and net gain, or adverse clinical events after coronary stenting were compared between the two study arms and expressed with the mean difference or odds ratios (OR) specific for the individual studies and meta-analytic pooled estimate for the mean difference or OR.

**Results:** Five of the clinical studies we reviewed met the inclusion criteria and underwent meta-analysis. The cilostazol was found to be superior in the pooled estimate of the total clinical outcomes and QCA as compared to ticlopidine (OR [95% CI]: 0.59 [0.46, 0.75]), MLD (WMD [95% CI]: 0.27 mm [0.17, 0.37]), late loss (WMD [95% CI]: -0.36 mm [-0.51, -0.22]), loss index (WMD [95% CI]: -0.16 [-0.24, -0.08]), and net gain (WMD [95% CI]: 0.49 mm [0.30, 0.68]). The pooled estimate of all adverse clinical events in cilostazol was approximately the same as that seen for ticlopidine.

**Conclusions:** Our results suggest that cilostazol plus aspirin therapy, as compared to ticlopidine plus aspirin therapy, might be superior with regard to long-term efficacy, particularly in preventing late restenosis. Although cilostazol exhibits few serious adverse events, we must paid attention to increased heart rate or occurrence of arrhythmias during treatments.

P-03

# Effects of dietary education to prevent type 2 diabetes mellitus: A meta-analysis

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**Objectives:** To evaluate the efficacy of dietary education program for preventing diabetes in groups of individuals at risk by a meta-analysis.

**Research design and methods:** The study design was a systematic review and meta-analysis of randomized control trials. All studies will include adult participants, who are diagnosed with high-risk for type 2 diabetes. The present study will address specifically the effects of interventions aimed at modifying dietary behavior. Difference from baseline to over 6 months of a level of plasma glucose 2 hours after a 75g oral glucose load (2hPG) was a main outcome measure. Difference in means was considered as the effect size of the present study. Combined estimates of the effect size were calculated using a fixed-effects model (variance-based method), two different random-effects models (DerSimonian-Laird and REML) and a Bayesian model using MCMC (WinBUGS).

**Results:** One hundred and twenty three studies were selected from electric search. Adding hand search results to this, finally 8 studies were selected for meta-analysis. As for the combined effects, the estimated effect size and it's 95% confidence interval were for fixed-effects model = (-0.704, -0.918～-0.490, $p<0.001$), DerSimonian -Laired = (-0.746, -1.261～-0.230, $p<0.01$), REML= (-0.752, -1.322～-0.181, $p<0.01$), and Bayesian method = (-0.781, -1.500～-0.027, $p<0.05$), respectively. Test for heterogeneity was statistically significant ($p<0.001$). Funnel plot gave us impression of no selection bias. The related factors of mean age, time at beginning of the study, baseline value of 2hPG and BMI seemed to have no associations with the effect size.

**Conclusions:** Dietary education program for reducing 2hPG in groups of individuals at risk should be effective and may be useful tool for preventing diabetes.

P-04

# DNA repair gene XRCC1 polymorphism and lung cancer risk among Chinese people: A meta-analysis

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Interindividual variation in lung cancer susceptibility may be moduled in part through genetic polymorphisms in the DNA repair genes. XRCC1 gene (X-ray cross-complementing group 1 gene) was implicated that may impact on lung cancer risk by altering DNA repair capacity in the base excision repair (BER) pathway. Only a few studies analyzed the relationship between lung cancer and XRCC1 gene polymorphisms. Single studies may have been underpowered to detect dose–response relationships or even overall effects because of small sample size. We performed a meta-analysis with the aim of obtaining summary estimates for the strength of its polymorphism. We considered all existing studies that examined the association of the XRCC1 polymorphisms with lung cancer. The racial descent of the population in these studies was Chinese. Sources included MEDLINE and CBMdisc (last search update was October, 2004). The results showed that there was no between-study heterogeneity in any of these analyses. It showed that there was no statistical association between susceptibility to lung cancer and 399 Gln allele (either the heterozygous Arg/Gln or the homozygous Gln/Gln genotypes). The OR is 1.339 (95%CI: 0.931-1.927) and 1.397 (95%CI: 0.715-2.729), respectively. While after the stratified analysis according to the pathological type, it showed that the 399Gln allele might increase the risk of lung adenocarcinoma (OR: 1.751, 95%CI: 1.036-2.960), and has no statistical relationship with lung squamous cells carcinoma (OR: 1.670, 95%CI: 0.896-3.112). Although bias cannot be excluded, the findings suggested that genetic polymorphism of XRCC1 DNA repair gene polymorphism at Arg399Gln loci might contribute to the susceptibility to lung adenocarcinoma.

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P-05

# The effect of history of tuberculosis on the risk of lung cancer

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**Objective:** To establish the effect of the history of tuberculosis on the risk of lung cancer.
**Methods:** The results from 11 eligible epidemiological studies about the effect of the history of tuberculosis on the risk of lung cancer were analyzed by Meta-analysis. The cumulative cases and controls are 5793 and 8830. This research divided all the studies into three subgroups, all population, women and non-smoking women. We use the Mantel-Haenszel of the fixed-effect model and DerSimonian-Laird(D-L) of the random-effects model to calculate the pooled ORs.
**Results:** The pooled OR value of all the population was 2.29(95%CI 0.87~6.05)based on 2257cases and 3256 controls; the pooled OR value of women was 1.53(95%CI 1.16~2.02); the pooled OR value of non-smoking women was 1.94(95%CI 1.36~2.77). With the smoking state was controlled, the effect of the history of tuberculosis on the risk of lung cancer was greater.
**Conclusion:** The history of tuberculosis is the risk factor of lung cancer, especially in non-smoking women..

**Key words:** tuberculosis lung cancer Meta-analysis
Supported by China Medical Board: No.00726

P-06

# Effect of smoking on hearing loss: Quality assessment and meta-analysis

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**Background:** There is an accumulating body of research showing that smoking causes hearing loss, however, the results of these studies have been inconsistent.
**Methods:** Original English articles were retrieved by MEDLINE search using key words "smoking" and "hearing" (1966-2003). Of 166 relevant studies, those that investigated the risk for hearing loss in smokers identified by pure-tone average were selected for review. Studies with an occupational noise-exposed population were excluded. Methodological quality was assessed by a standardized checklist, and then a meta-analysis was performed on studies with discrete numbers of hearing loss among smokers and non-smokers.
**Results:** A total of 15 (10 cross-sectional, 4 cohort, and one case-control) were identified; the quality scores of the 9 studies with positive associations between smoking and hearing loss were comparable to those of the remaining 6 studies with insignificant associations. Concerning 8 analyzable studies, risk ratios (95% confidence intervals) for hearing loss in smokers were 1.33 (1.24, 1.44) for cross-sectional studies, 1.97 (1.44, 2.70) for cohort studies, and 2.89 (2.26, 3.70) for case-control studies, respectively.
**Conclusions:** The evidence was suggestive of a positive association between smoking and hearing loss. It is possible that smoking cessation may be a useful strategy for maintaining hearing acuity.

P-07

# Blood levels of vitamin C and the subsequent risk of Stroke in cohort studies: A systematic review

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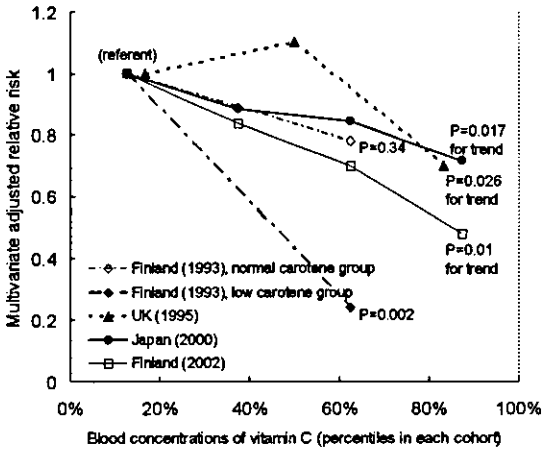
**Background and purpose:** There has been a growing interest in the potential role of antioxidative vitamins for the prevention of cardiovascular disease. At least 3 large randomized controlled trials are on-going in the U.S. (WACS and Physicians' Health Study II) and France (SUVIMAX study) to assess the effects of antioxidative vitamins, including vitamin C (VC), for the prevention of stroke. However, the findings from observational studies, especially those based on dietary surveys, are inconsistent. The purpose of the present study is to systematically review the relationship between blood levels of VC and the subsequent risk of stroke (VC-stroke relationship) in observational cohort studies.

**Methods:** Cohort studies assessing the VC-stroke relationship were identified by a MEDLINE search with key words: cohort studies[MeSH] AND (ascorbic acid[MeSH] OR ascorbic acid[tw] OR ascorbate[tw] OR vitamin c[tw]) AND (cerebrovascular disease[MeSH] OR stroke[tw]), in March 3, 2004.

**Results:** Four cohort studies were identified: two studies in Finland, a study in Japan, and a study in the U.K. Two studies analysed data by subtypes of stroke and the other 2 studies analysed for all strokes combined. Blood levels of VC were categorized by the quartiles in 2 studies, tertiles in a study, and 'low' vs. 'high' (a cut-off point of 22.7μmol/L) in a study. A significant dose-response VC-stroke relationship was observed in 3 studies; and the other one reported an increased risk of stroke only when blood levels of VC and beta-carotene were simultaneously low (Figure).

Figure. Blood concentrations of vitamin C and the subsequent risk of stroke in 4 cohort studies




**Conclusions:** Observational cohort studies consistently showed a strong inverse VC-stroke relationship, however, the number of available studies was limited.

P-08

# Comparison of effects in randomized, controlled trials with observational studies in digestive surgery

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**Background:** While randomized, controlled trials have been recognized as providing the highest standard of evidence, claims have been made that observational studies may overestimate treatment benefits. This debate has recently been renewed, particularly with regard to pharmacotherapies. To extend perspectives, the present study compared the results of identical meta-analyses (randomized, controlled trials versus observational studies) on digestive surgical topics.

**Methods:** The PubMed, EMBASE and Cochrane databases were searched to identify meta-analyses of randomized, controlled trials in digestive surgery that had been published up to 2004. We then undertook an exhaustive search of the observational studies for all selected topics and combined various extracted data for every outcome. Summary estimates from randomized, controlled trials were compared with observational studies under equivalent conditions to the maximum extent possible.

**Results:** This investigation identified 52 outcomes of 18 topics from 276 original articles with a total of 101,170 study participants. Significant between-study heterogeneity was seen more often among observational studies than among randomized, controlled trials (7 of 14 topics vs. 1 of 11 topics, respectively;). In 48 of 52 outcomes compared (9 of 10 primary outcomes), summary estimates of treatment effects were similar.

**Conclusions:** Meta-analyses of observational studies were not found to overestimate treatment effects relative to randomized, controlled trials in the field of digestive surgery.

P-09

# The quality of reporting of randomized controlled trials conducted in Japan: An evaluation based on the consort statement

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Randomized controlled trials (RCTs) is a means of ensuring the highest scientific validity, and provides essential information for systemic reviews and meta-analyses. They are best used as a source of information, only if researchers conduct and report them with the utmost quality. This study evaluates the quality of RCT reporting from Japan, based on the CONSORT statement.

This study is a descriptive literature review, targeting the RCT reported from Japan. All reports were published in January and March, 2004 and registered to PubMed. Evaluation was based on the CONSORT statement (32 items) and original 3 items: IRB review, informed consent, conflict of interest. A cross-tabulation was used between evaluative item and whether or not the accepting journals supported the CONSORT statement.

The total of 100 reports was reviewed, of which 10 supporting CONSORT, 90 not supporting CONSORT. Among 32 CONSORT items, the mean number of items described was 15 (16.5 items in journals supporting CONSORT, and 15 items in journals not supporting CONSORT). IRB, informed consent, and conflict of interest were described in 83, 92, and 19 reports, respectively.

The quality of reporting of RCTs from Japan is not adequate and further improvement is needed. Having journals comply with the CONSORT statement alone is not sufficient in improving the quality. Further education on international guidelines such as the CONSORT statement are anticipated, and both researchers and writers, should be encouraged to follow them.

(Tentative report as of January 8, 2005. Final analysis is to be completed by February, 2005.)

P-10

# A meta-analytic comparison of echocardiographic stressors

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**Background:** The relative performance of alternative stressors for stress echocardiography for the diagnosis of coronary artery disease (CAD) is not well established.

**Methods:** All studies published between 1981 to December 2001 who met inclusion criteria were included in this analysis. We performed a summary receiver operator characteristic (SROC) analysis and calculated weighted mean of the likelihood ratio and sensitivity/specificity. A covariate analysis using meta-regression methods was also performed.

**Results:** Forty-four studies presented data on Exercise, 11 on Adenosine, 80 on Dobutamine, 40 on Dipyridamole, 16 on transatrial pacing transesophageal echocardiography (Tap-TEE), and 7 on transatrial pacing transthorasic echocardiography (Tap-TTE). Summary receiver operator characteristic (SROC) analysis showed that the following order of most discriminatory to least: Tap-TEE, Exercise, Dipyridamole, Dobutamine and Adenosine. Weighted means sensitivity/specificity were Exercise: 82.6/84.4 %, Adenosine: 68.4/80.9 %, Dobutamine: 79.6/85.1 %, Dipyridamole: 71.0/92.2 %, Tap-TTE: 90.7/86.1 %, and Tap-TEE: 86.2/91.3 %. Covariate analysis showed that the discriminatory power of Exercise decreased with increasing mean age.

**Conclusions:** Tap -TEE is a very accurate test for both ruling in and ruling out CAD although its invasiveness may limit its clinical acceptability. Exercise is a well-balanced satisfactory test for both ruling in and ruling out but performance might be lower for the elderly. Dobutamine offers a reasonable compromise for Exercise. Dipyridamole might be good for ruling in but not for ruling out CAD. The incapability in ruling-out CAD was a major problem in clinical application of the stress. Adenosine was the least useful stressor in diagnosing CAD.

# Does neuromuscular electrical stimulation strengthen the quadriceps femoris? A systematic review of randomized controlled trials

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**Background:** Devices for neuromuscular electrical stimulation are increasingly used by individuals without specific injuries and are standard equipment in most physical therapy practices. The most often stimulated muscle group is the quadriceps femoris. We designed a systematic review and meta-analysis of randomized controlled trials to determine whether neuromuscular electrical stimulation is an effective modality for strength augmentation of the quadriceps femoris.

**Methods:** A full content search for randomized controlled trials was performed in Medline, Embase, Cinahl, the Cochrane Controlled Trials Register, and the Physical Therapy Evidence Database. Maximum volitional isometric or isokinetic muscle torque in Newton-meter was used as main outcome measure.

**Results:** Thirty-five trials were included and evaluated. A fundamental distinction was made between the trials using subjects with unimpaired quadriceps femoris muscles and the trials using post-injury or post-operative subjects. In the unimpaired quadriceps subgroup, meta-analyses were performed for the comparisons 'NMES versus no exercises' and 'NMES versus volitional exercises'. All other comparisons were evaluated descriptively. The included trials were generally of poor quality and meta-analytic data indicate that publication bias may be present. The evaluated data suggest that, both for the unimpaired and impaired quadriceps, NMES makes sense compared to doing no exercises but volitional exercises appear to be more effective in most situations.

**Conclusions:** Based on the available evidence, neuromuscular electrical stimulation may only be preferred over volitional training for within-cast muscle training and perhaps in specific situations where volitional training does not receive sufficient patient compliance. Further research should be directed toward identifying the clinical impact at activity and participation levels and the optimal stimulation parameters of this modality.

P-12

# The 'MIX' program, an active way of learning about meta-analysis with Excel

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**Background:** Currently, various programs are available for performing meta-analyses. Some are relatively cheap and user-friendly, whereas others are expensive and difficult to use. Even though the number of researchers getting involved in systematic reviews and meta-analyses has grown exponentially in the last decade, there are no statistical programs available that are specifically aimed at educating inexperienced users about what they are doing. Our objective was therefore to fill this niche and to develop a program that could assist those new to meta-analysis in learning about them in a practical, interactive way.

**Methods:** We started with assessing recent articles about meta-analysis methodology and created a list of all statistical calculations and procedures to be integrated in the program. Ease of use, interactive learning, and flexibility for adding additional options were chosen as central themes for the actual development. Output is being verified with various professional statistical programs.

**Status:** In contrast to other developers of programs for meta-analysis so far, we decided not to make a stand-alone program, but an add-in for Excel. This has resulted in a familiar working environment for inexperienced users and has allowed us to make use of some of the extensive calculational potential in Excel. To allow the users to learn about "what is what?" and "what is it for?" an extensive Concept Tutor and a Statistics Assistant has been developed with Visual Basic for Applications and can be consulted from within the program. With this interactive learning as primary theme, we named the program MIX: Meta-analysis with Interactive eXplanations. In the current version (part of the development is still ongoing) meta-analyses can be performed with built-in data sets of existing published meta-analyses or with personal data sets created with the data set wizard. It features fixed and random effects analyses and allows the calculation of pooled risk differences, risk ratios, odds ratios, weighted mean differences and weighted Hedges' Gs, based on per group input or comparative input, the latter being analyzed by generic inverse variance methodology. For assessment of heterogeneity as well as publication bias, various test options are available. Current graphical output includes standard and cumulative forest plots, multiple funnel (regression) plots, a Galbraith plot, a L'Abbe plot, an exclusion sensitivity plot, and more.

**Conclusion:** A beta-version for final testing will be available early 2005 and with the official launch some time later in 2005, we expect the program to become a helpful tool for researchers and clinicians interested in learning about and performing meta-analyses.

P-13

# Concerns encountered in the meta-analysis of the causal relationship between coffee consumption and type 2 diabetes

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A prophylactic effect of coffee on type 2 diabetes was reported in 2002 by a Dutch research group. Since then, four prospective cohort studies have presented data on the same topic. All the information finally reached more than 160,000 participants. Insulin secretion by caffeine is considered as a possible mechanism. We performed a meta-analysis on this topic. In the process of this work, we encountered several difficulties to perform the meta-analysis. In this presentation, these are exposed to the audiences of this symposium.

As usual, each article reported an adjusted risk (accurately speaking, odds ratio) and its 95% confidence interval. To combine these reported risk data across the studies, we utilized an inverse variance weighting method. The first issue was that there was inconsistency in the control group with respect to the amount of coffee consumption. Three studies specified the control group to be 2 cups or less; one study set the control to be no coffee drinkers; one study set the control to be 1 cup or less. We determined 2 cups or less as the control group since it was a majority and included coffee consumption of 1 or 0 cup. Second, the risk of developing diabetes was assumed to be linearly decreased upon coffee consumption, although we do not know whether a linear trend is valid. The last issue was that categorization of the amount of coffee consumption was variable among the studies and reported the data for the interval of coffee consumption such as 3 – 4 cups per day. For the cases reported 3 – 4 cups per day, we supposed the risk for 3.5 cups a day. A further problem was how to deal with the last category of coffee consumption that was censored such as 6 cups or more. In any event, several assumptions were necessary to overcome the variability in data presentations among the studies in conducting a meta-analytic research on this topic.

# Confidence intervals for the ratio of regression slopes in meta-analysis

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In epidemiological studies of the association between disease and exposure to some agent or hazard, it is often of interest to estimate how much risk increases as exposure increases. Studies that measure the risk at different levels of exposure are usually analysed by trend estimation using linear regression analysis. For instance, we assume that blood pressure $y$ has a relationship with alcohol consumption $x$. This simple linear regression model is

$$y = \alpha + \beta x + \varepsilon ,$$

where $\varepsilon$ is a random error component according to normal distribution $N(0, \sigma^2)$. It can be assumed therefore that another factor (ex. genotypes) may associate with individual differences in sensitivity to alcohol toxicity including the pressor effect, that is, they have the slope $\beta_1$ for type 1 and $\beta_2$ for type 2 respectively and we have an interest in the ratio of slopes

$$\rho = \frac{\beta_2}{\beta_1} .$$

Confidence intervals of $\rho$ are derived from the data by Fieller's theorem.

Meta-analysis is used to combine together the evidence from several such studies. However, meta-analyses of observational studies often have to rely on the limited data available from research reports. In such cases, it is difficult to estimate $\rho$ and to derive its confidence intervals in regression analysis.

In this study, we suppose cases that we can get several descriptive statistics for each grouped $x$ as follows

| | Type1 | | | Type2 | | |
|---|---|---|---|---|---|---|
| $x$ | No. of cases | Mean of $y$ | S.E. | No. of cases | Mean of $y$ | S.E. |
| $(I_0, I_1]$ | $n_1$ | $\bar{y}_1$ | $se_1$ | $n_1'$ | $\bar{y}_1'$ | $se_1'$ |
| $(I_1, I_2]$ | $n_2$ | $\bar{y}_2$ | $se_2$ | $n_2'$ | $\bar{y}_2'$ | $se_2'$ |
| $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ | $\vdots$ |
| $(I_{m-1}, I_m]$ | $n_m$ | $\bar{y}_m$ | $se_m$ | $n_m'$ | $\bar{y}_m'$ | $se_m'$ |
| Total | $N$ | | | $N'$ | | |

and means and variances of $x$ for each type. Then we try to estimate $\rho$, standard error of an estimator $\hat{\rho}$ and to derive its confidence intervals. We also describe statistics that is necessary to reconstruct the ratio of slopes for meta-analysis.

P-15

# Meta-analysis of low does radiation risk: An application of meta-regression model to biological risk evaluation

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Linear non-threshold (LNT) model is a basic theory for radioprotection, but the adaptability of this hypothesis to biological responses at low doses or at low dose rates is not sufficiently investigated. In this study, we acquired quantitative experimental data at low doses/low dose rates using micronucleus formation of human osteosarcoma as biological reaction to low dose gamma radiation. To estimate "observed minimum risk level" (OML) of the response for cells irradiated at low doses with a variety of dose rates, we applied meta-regression models to the data and compared them with other statistical models that find values corresponding to "threshold limits".

By fitting a weighted regression model (fixed-effects meta-regression model) to the data, it was found that the log relative risk [log(RR)] decreases as the total exposure dose decreases. The intersection of this regression line with the x-axis denotes the OML. However, as the heterogeneity is present beyond that explained by the total exposure doses, we applied mixed model that includes random-effects considering residue heterogeneity. The confidence intervals of estimated OMLs for mixed model are wider than those for fixed-effects model. Therefore when residue heterogeneity is present, above that explained by doses, it is difficult to find a "threshold". These estimated OMLs remarkably increased with an increase of irradiation time, this shows that the risk is reduced when dose rates are very low. These results suggest that dose response curve of biological reaction is remarkably affected by exposure time, and that dose rate effect changes as a function of dose-rate and irradiation time. Moreover, OMLs and their confidence intervals depended on models used for the estimation.

For scientific discussion on the low dose exposure risk and its uncertainty, the term "threshold" should be statistically defined, and dose rate effects should be included in the risk evaluation model.

P-16

# Method of correcting for publication bias in meta-analysis

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The publication bias, the tendency the researches with statistically significant results is more likely to be submitted and to be published than the researches with non-significant results, is a very serious problem in meta-analysis. The most serious consequence of this bias would be an overestimate of treatment effect and lead to an inappropriate decision about the selection of treatment or health policy. Several statistical methods for publication bias have been studied.

The trim-and-fill[1] method was proposed by Duval and Tweedie (2000). This method estimates the number of unpublished studies, based on the property of the funnel plot. The funnel plot is a scatter plot sample size versus treatment effect (eg. log odds ratio) of individual study in a meta-analysis. The shape of this plot like an inverse funnel if there is no publication bias. But, if the probability of publication of studies with positive statistically significant results is greater, the shape of the funnel plot may be skewed and asymmetric. Consequently, the trim-and-fill method estimate the number of studies to be needed for recovering the shape of the funnel plot 'asymmetry' to 'symmetry', then estimate the true effect size based on the artificially symmetrized funnel plot. But, the mechanism of publication that is assumed in the trim-and-fill method is unrealistic, therefore this method could not correct for publication bias appropriately.

Therefore, the new method to correct for publication bias is proposed. Our method assumes that the probabilities of publishing are based on the p-value of individual study in a meta-analysis, and the weight of each study is defined as an inverse of the probability of publishing, then calculate the weighted average for estimating the combined effect.

A simulation study is performed to compare the performance of the proposed method with that of the trim-and-fill method.

**Reference:** [1] Sue Duval and Richard Tweedie., "A Nonparametric "Trim and Fill" Method of Accounting for Publication Bias in Meta-Analysis". Journal of American Statistical Association. 2000; Vol.95, No.499: 89-97

P-17

# Development of a Clinical Trials Registry in Japan

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4. Clinical Trial Support Center of Showa University Hospital

**Background:** The needs of the clinical trials registry (CTR) have been discussed, and several projects have started since the 1990s, although they have not been quite satisfactory. After the anti-depressant scandal in New York in June 2004, awareness has rapidly grown and global discussion of the topic as well as a new CTR project was initiated by concerned groups. Presently, however, the situation is still fluid and somewhat chaotic. This study aims to review the global status of CTR and introduce the UMIN-CTR, which is the first attempt to develop the CTR system in Japan using public funds.

**Methods:** Literature search, internet search, meetings, and interviews with relevant key persons.

**Results:** The following key global events after the year 2000 led to a growing concern about a more comprehensive clinical trials registry: (1) 2000: Amendment to the Declaration of Helsinki, calling for the publishing of or making public both positive and negative data; (2) June 2004: GSK's scandal on the use anti-depressants for children; (3) September 2004: Statement from the International Committee of Medical Journal Editors (ICMJE) on requiring a registry of clinical trials; (4) October 2004: Ottawa meeting on CTR during the 12th Cochrane Colloquium; (5) October 2004: WHO International Registry Platform Meeting in New York; (6) November 2004: Ministerial Summit on Health Research at Mexico City; (7) January 2005: International Federation of Pharmaceutical Manufacturers Association (IFPMA) statement.

In Japan, a Working Group on CTR was established in October 2004 to develop policy and discuss technical issues on UMIN-CTR. A symposium on CTR to introduce an alpha version of it and to have public comments was held on 2 February 2005. The system is

currently under revision [http://www.umin.ac.jp/ctr/index-j.htm]. Full implementation is scheduled to start in April 2005.

A wide range of opinion was observed both globally and domestically. Ethics, ensuring compliance, and the role of government were among the hot topics.

**Conclusion:** Close collaboration with international agencies, including WHO, as well as internal collaboration within Japan is strongly recommended for more comprehensive and user-friendly system development.

# 招待講演者の講演資料

**I-01** Uses and impact of systematic reviews and meta-analyses on clinical practice and healthcare
***Professor Joseph Lau (Tufts-New England Medical Center, USA)***

**I-02** Meta-analysis in molecular medicine
***Professor John P.A. Ioannidis (University of Ioannina, Greece)***

**I-03** The issue of indirect comparisons in meta-analysis
***Professor Douglas G Altman (Center for Statistics in Medicine, UK)***

**I-04** Graphical displays that might be helpful in interpreting medical data
***Professor Ingram Olkin (Stanford University, USA)***

Uses and impact of systematic reviews and meta-analyses on clinical practice, medical research and health policies

Joseph Lau, MD

February 25, 2005
International Symposium:
Systematic Review and Meta-Analysis
Tokyo, Japan

Evidence-based medicine should be based on evidence

Rating of the evidence is an essential part of a systematic review to convey to the readers the essence of the information

A proposal

All lectures should be rated

My talk is rated "G"

- It is appropriate for all ages and all levels of statistical knowledge
- The use of the "S" word is avoided
- There are no equations or graphical depictions of statistical analyses to cause you discomfort

Prof. John Ioannidis
Meta-analysis of molecular medicine

- "M", for the methodological mature audience
- M is also for "madness" and his intellectual brilliance is breaking new grounds in this area

Profs. Altman and Olkin
Indirect comparisons / Graphical display

- "S" – statistically interested audience
- They are most stimulating
- Depicts graphically statistical analyses
- However, if you are offended by statistics, you may close your eyes and fall asleep discreetly at appropriate moments; but please don't snore for the benefit of your neighbor