資料-1. 国際シンポジウム
システマティック・レビューとメタ・アナリシス
International Symposium on Systematic Review and Meta-Analysis

本研究班では、平成16年度の研究成果の発表会を兼ねるとともに、欧米のシステマティック・レビューとメタ・アナリシスの分野の第一人者の協力を得て、日本におけるメタ・アナリシスの普及のための事業として、（財）日本救急医療財団、医療技術評価総合研究推進事業研究成果等普及啓発事業へ下記の内容の研究成果発表の申請を行って国際シンポジウムが開催された。

成果発表会申請内容の概要

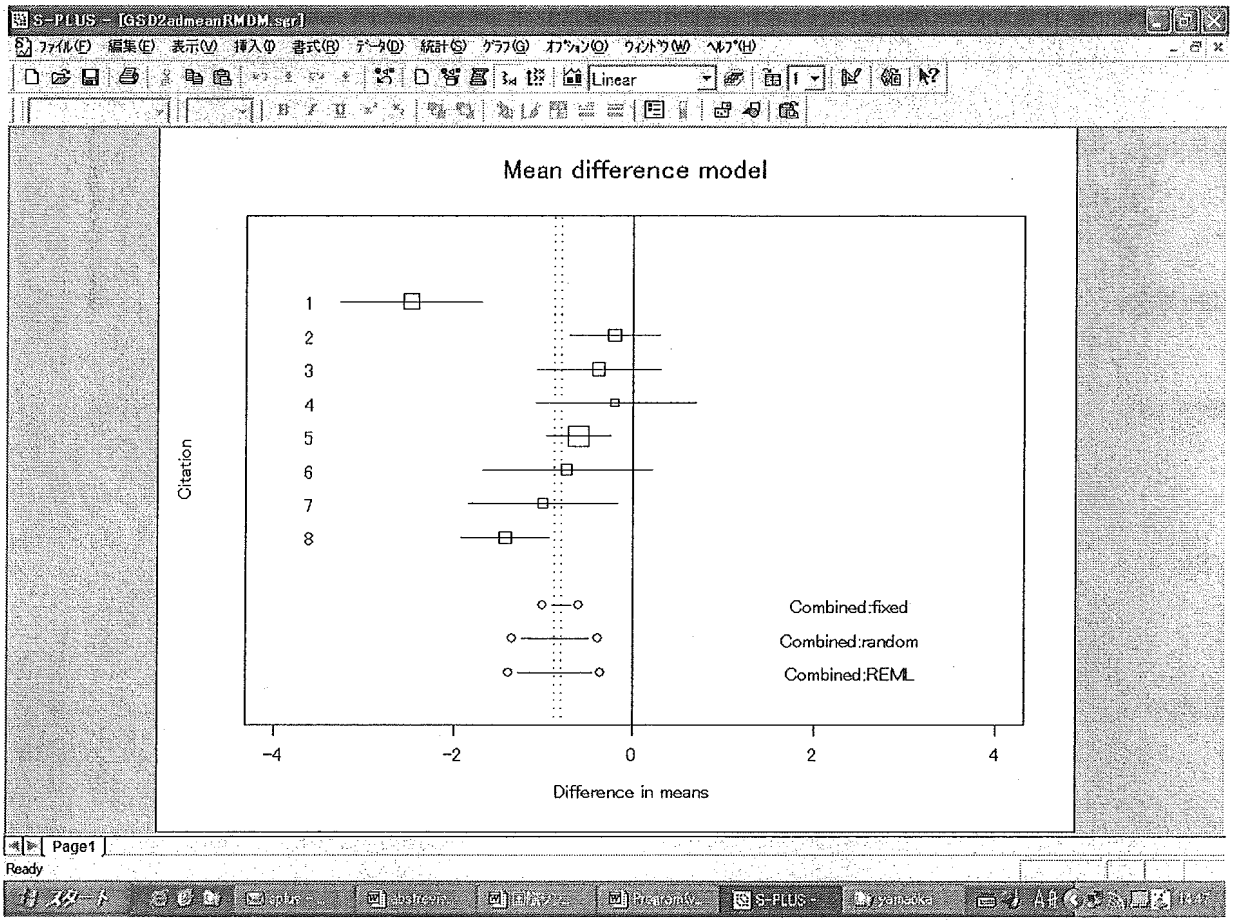
１．主任研究者氏名　　丹後 俊郎
　（所属機関）　　国立保健医療科学院
２．主任研究者の研究課題
　エビデンスを適切に統合するメタ・アナリシスの理論、応用と普及に関する調査研究
３．研究成果発表会のテーマ
　国際シンポジウム「システマティック・レビューとメタ・アナリシス」
４．研究成果発表会の開催日時
　日時：平成１７年２月２５日、８時３０分～１７時３０分
　場所：国立保健医療科学院 講堂

シンポジウムの参加者数は当日の降雪の交通機関の乱れにもかかわらず140名であった。発表者は招待講演４題、一般発表（ポスター）17題であった。

International Symposium of

"Systematic Review and Meta-Analysis"

Abstracts



25 February 2005
National Institute of Public Health (NIPH)
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February 2005

Dear Participants in this Symposium,

Welcome to Wako and the 2005 International Symposium: Systematic Review and Meta-Analysis ! I very much hope you will find the experience of the single-day-symposium enjoyable, as well as rewarding intellectually and professionally.

The symposium is designed to address current issues on meta-analysis by inviting the world foremost experts on systematic review and meta-analysis for technology assessment of health care. The meeting will also provide Japanese researchers with an opportunity for an exchange of ideas that will help accelerate current research, development and diffusion of meta-analysis and EBM.

I would like to thank four world leaders, Joseph Lau, John Ioannidis, Doug Altman and Ingram Olkin for their kind acceptance as invited speakers. Thanks also go to organizing committees together with symposium secretariat Yoko Nezu for their hard work and dedication in putting this international symposium together.

With best wishes for a most stimulating symposium

Toshiro Tango
Chair, Organizing Committee
Department of Technology Assessment and Biostatistics
National Institute of Public Health, Japan

International Symposium: Systematic Review and Meta-Analysis
Organizing Committee

Toshiro Tango (Chair)	National Institute of Public Health, Japan
Joseph Lau	Tufts-New England Medical Center, USA
Yoshinori Noguchi	Fujita Health University, Japan
Hideki Origasa	Toyama Medical and Pharmaceutical University, Japan
Kiichiro Tsutani	Graduate School of Pharmaceutical Sciences, the University of Tokyo, Japan
Kazue Yamaoka	National Institute of Public Health, Japan

Partnership:

Japan Council for Quality Health Care (JCQHC)
Japan Foundation for Emergency Medicine (JAFEM)
Japan Statistical Society (JSS)
Japanese Society for Pharmacoepidemiology (JSPE)
The Behaviormetric Society of Japan (BSJ)
The Biometric Society of Japan (JBS)
The Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT)
The Japanese Society of General Medicine (JSGM)

Program

8:30 am Registration opens

Time for displaying poster (8:30 am - 9:15 am)

9:15 am - 9:25 am Opening address *Tango T, NIPH.*
9:25 am - 9:30 am Welcome address *Shinozaki H, President of NIPH.*

Session I : Invited Session (I)
Chair. *Tsutani K, Graduate School of Pharmaceutical Sciences, the University of Tokyo, Japan.*

9:30 am - 10:35 am Uses and impact of systematic reviews and meta analyses on clinical practice and healthcare.
Lau J, Tufts-New England Medical Center, USA.

10:35 am - 11:40 am Meta-analysis in molecular medicine.
Ioannidis J, University of Ioannina School of Medicine, Greece.

11:40 am - 11:50 am Compliments *Shimmura K, Ministry of Health, Labor and Welfare, Japan*

Lunch and looking at poster displays (11:40 am - 1:00 pm)

Session II : Invited Session (II)
Chair. *Origasa H, Toyama Medical and Pharmaceutical University, Japan.*

1:00 pm - 2:05 pm The issue of indirect comparisons in meta-analysis.
Altman D, Centre for Statistics in Medicine, Oxford, UK.

2:05 pm - 3:10 pm Graphical displays that might be helpful in interpreting medical data.
Olkin I, Stanford University, USA.

Session III : Panel discussion and floor discussion
Chair. *Tango T, NIPH.*
3:15 pm - 4:00 pm
Panelists. *Lau J, Ioannidis J, Altman D, and Olkin I.*
Interpreter. *Misago C, Tsuda College, Japan.*

Coffee Break (4:00 pm - 4:20 pm)

Session IV : Poster Sessions (Free discussions)
4:20 pm - 5:40 pm

6:00 pm - 8:00 pm Get-together party (at Restaurant, NIPH)

Invited Papers

Contributed Papers (Posters)

I-01

Uses and impact of systematic reviews and meta-analyses on clinical practice and healthcare

Joseph Lau, MD

Tufts-New England Medical Center, USA

The term "Evidence-Based Medicine (EBM)" was coined about a decade ago and it rapidly became a global phenomenon. EBM has attracted the interest of a diverse spectrum of people including researchers, clinicians, educators, students, patients, and healthcare policy decision makers. Systematic reviews and meta-analyses are the foundation on which EBM is based. These methodologies were developed in response to the growing needs of clinicians and researchers faced with the problem of the biomedical literature explosion. Many lacked the time to keep up with the ever-growing body of literature and the skills and resources necessary to synthesize and interpret this information.

A Google search performed on January 23, 2005 using the term "evidence-based medicine" found 1,190,000 items, 925,000 items for "systematic review," and 1,680,000 items for "meta-analysis." Even if only a fraction of these items are related to medicine or healthcare, the number of items found on the Internet rivals the number of primary research articles that systematic review and meta-analysis are supposed to address. EBM is not limited to medicine; it is gaining acceptance in other related healthcare fields such as dentistry, nursing, nutrition science, veterinary medicine, and health policy. People from many countries now participate in various types of EBM activities. The Cochrane Library is the best-known example of successes in systematic review and meta-analysis and an exemplary model of international collaboration.

Thousands of systematic reviews and meta-analyses have been published on healthcare interventions, evaluations of diagnostic tests, assessments of risks and prognosis. Many of these articles are published in high-ranking medical journals and many of these reviews have generated headline news and are affecting daily clinical decisions and healthcare policies. In the process, these publications have also influenced medical research agenda. Many professional organizations use systematic reviews in the development of clinical practice guidelines.

Systematic reviews are increasingly being used by government organizations as the evidentiary basis to inform healthcare policies and guide future research agenda. In the United

States, as an example, the FDA commissions systematic reviews to evaluate food health claims, the Center for Medicare and Medicaid Services (CMS) uses evidence reports and technology assessments to guide healthcare reimbursement decisions. The NIH Consensus Development Conferences now regularly relies on comprehensive evidence reports as part of the conference process. Many other countries use systematic reviews and meta-analyses similarly.

The impact of systematic reviews and meta-analyses is just beginning to be felt. It is relatively easy to demonstrate that a specific intervention saves or improves lives but it is difficult to do so for a systematic review or a meta-analysis. However, several striking examples such as pre-natal use of corticosteroids to reduce mortality in premature births and intravenous thrombolytic therapy for acute myocardial infarction offer glimpses of the potential values of meta-analyses conducted in a timely manner.

Successes notwithstanding, there are critics of meta-analysis. Some of their criticisms have been addressed in the past decade with the development of new methods and empirical research in systematic review and meta-analysis. These efforts have led to a better foundation for understanding of heterogeneity, metrics, and interpretation of meta-analysis results. Recommendations from this body of research hopefully will also lead to better conduct and report of primary research. The advent of human genomics presents new challenges in summarizing and interpreting a large and diverse body of information. In the future, systematic reviews and meta-analyses must also be produced in real time to increase their usefulness and impact.

Meta-analysis in molecular medicine

John P.A. Ioannidis, MD

Professor and Chairman, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; Professor of Medicine (adjunct), Tufts University School of Medicine, Boston, USA

Meta-analysis is currently finding a widening circle of applications in molecular medicine. The rapid advent of technology in the basic sciences has generated very interesting challenges for the integration of biomedical information. Meta-analysis can help to make sense of the rapidly accumulated data and may be a useful link in the translation of this basic information to meaningful results and clinical use. Meta-analysis can also be a prime tool for dissecting biases and other sources of heterogeneity in these data. Several of the biases in this literature are similar to what is already known from the more traditional literature of clinical research. There are however also additional problems that stem from peculiarities of specific molecular science fields. The talk will try to cover some of the most promising applications of meta-analysis in molecular medicine, including genetics and genomics, predictive biomarkers, and microarrays. Special emphasis will be given to issues of heterogeneity and bias, including differences in early vs. subsequent research, rapid alternation of extreme results (Proteus phenomenon), small vs. large studies, standardization issues, outcome reporting biases, language bias, impact of measurement error (e.g. deviation from Hardy-Weinberg equilibrium in genetic association studies), empirical evidence on ancestry effects and other subgroup differences, validation challenges, and issues in the clinical interpretation of the results. We will also discuss the advantages and disadvantages of evolving concepts such as meta-analysis of individual participant data, study registration, data collection/investigator registration, and the creation of multicenter international networks in this field. Finally, a scheme for grading the evidence in molecular research will be proposed.

The issue of indirect comparisons in meta-analysis

Douglas G Altman

Centre for Statistics in Medicine, Oxford, UK

Background:

The randomised controlled trial (RCT) is the most valid design for evaluating the relative efficacy of health care interventions. However, many competing interventions have not been directly compared in RCTs. For example, each of two drugs may have been compared to placebo in RCTs but they have not been compared directly. A comparison based on comparing two sets of trials is known as an 'indirect' comparison.

Indirect methods are common in meta-analyses, but they are subject to greater bias (especially selection bias) than 'head-to-head' randomised comparisons, as the benefit of randomisation does not hold across trials. An equivalent problem arises when we wish to compare two subsets of trials within a meta-analysis, for example based on trial characteristics, study quality, or the precise interventions (e.g. dose). It is important to understand the additional issues that arise in such analyses as they may lead to inaccuracies in the estimates of treatment effects and result in inappropriate policy decisions.

This talk will discuss the findings of a large project[1,2] with the following objectives:

- To survey the frequency of use of indirect comparisons in systematic reviews and evaluate the methods used in their analysis and interpretation
- To identify alternative statistical approaches for the analysis of indirect comparisons and assess their properties
- To carry out empirical work comparing direct and indirect estimates of the same effects within reviews.

Methods:

(a) The Database of Abstracts of Reviews of Effectiveness (DARE) was searched for systematic reviews involving meta-analysis of RCTs which reported both direct and indirect comparisons, or indirect comparisons alone.

(b) A systematic review of Medline and other databases was made to identify published methods for analysing indirect comparisons.

(c) A resampling study was carried out using data from the large International Stroke Trial. Results of indirect comparisons were compared with direct comparisons and also theoretical results.

Results:

Of systematic reviews that included meta-analyses of two or more RCTs, 31/327 (9.5%) included indirect comparisons. Few studies had carried out a formal analysis. Some reviews based analysis on the naïve addition of data from the treatment arms of interest. Interpretation of indirect comparisons was not always appropriate.

In most cases, results of adjusted indirect comparisons mostly agreed reasonably well with those of direct comparisons. A significant discrepancy ($P < 0.05$) was observed in just three of the 44 comparisons between the direct and the adjusted indirect estimates. The direction of discrepancy between the two estimates was inconsistent.

Rather few relevant methodological papers were identified. The resampling study showed that the naïve method is liable to severe bias and also produces over-precise answers. Several other methods will be described that provide correct answers, although they rely on strong but unverifiable assumptions inherent in the indirect framework. Four times as many similar sized trials are needed for the indirect approach to have the same power as directly randomised comparisons.

Conclusions:

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good quality RCTs should be used wherever possible. When there is no or insufficient direct evidence from RCTs, the adjusted indirect comparison may provide useful or supplementary information on the relative efficacy of competing interventions.

Several valid methods of analysis exist for making adjusted indirect comparisons, but interpretations should be more cautious in view of the observational nature of the data. The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials. Adjusted indirect comparisons usually but not always agree with the results of head-to-head randomised trials. If both direct and indirect comparisons are possible within a systematic review, these should be done separately before considering whether to pool data.

Song F, Altman DG, Glenny A-M, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326:472–474.

Glenny A-M, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, Bradburn M, Eastwood A. Indirect comparisons of competing interventions. *Health Technology Assessment*, in press

Graphical displays that might be helpful in interpreting medical data

Ingram Olkin

Stanford University, USA

The primary output in almost all medical meta-analyses is a diagram that displays the confidence intervals for treatment-control comparisons for each study, together with a combined confidence interval for the overall effect. When there are important subgroups, as for example, sex differences or age categories, there will also be a combined effect within the subgroups. In general the measures of treatment-control effects are based on standardized mean differences for continuous data and risk differences, odds ratios, or risk ratios for proportion data.

These studies also provide considerable data on the demographics of the samples. Some studies will use a regression model to take account of these demographic variables. However, the relationship among the demographic variables and their relation to the outcome measures has not been well-understood. Because of the advances in computational power, visual maps can be created that display these relationships. These maps often help in the interpretation of the data. In this talk we show one particular method that is based on multidimensional scaling methodology, and apply it to explore the relationships among the studies of quality improvement for diabetes. The primary purpose of multidimensional scaling is to develop a map that represents the proximities between observations or events. Medical applications of this methodology has primarily been in cancer genetics: assaying the relationship between multiple proteins, genes, or patient characteristics and tumor characteristics.

Diagnostic data provides another area in which visualization can be useful, especially in the use of resampling methods to provide confidence bands for ROC curves. A particular example deals with the accuracy of calcaneal quantitative ultrasound as a diagnostic criterion for osteoporosis.

P-01

Bibilometric study of meta-analysis literatures, 1990-2003

Nozoe A

Graduate School of Library and Information Science, Aichi Shukutoku University

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

Hashiguchi M[1], Ohno K[2], Kishino S[2], Mochizuki M[1], Shiga T[3]

1 School of Pharmaceutical Sciences, Kitasato University
2 Meiji Pharmaceutical University
3 Tokyo Women's Medical University, Japan

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

Yamaoka K and Tango T

Department of Technology Assessment and Biostatistics, National Institute of Public Health

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

Huang Desheng, Guan Peng, He Qincheng, Zhou Baosen

China Medical University, Shenyang, 110001, China

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.

Supported by: China Medical Board (00726) and National Natural Science Foundation of China (30471493)

P-05

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

Zhou Baosen , Jiang Donghua, He Qincheng

Department of Epidemiology, China Medical University

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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Takeshi Morimoto, M.D., M.P.H. [2]

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2 Department of General Medicine and Clinical Epidemiology, Kyoto University Hospital and Graduate School of Medicine

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.