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General Summary

Our major research projects in the 2010 academic year focused on: 1) induction of micronuclei and chromosome aberrations in human peripheral blood lymphocytes from workers exposed to indium tin oxide; 2) examination of the chromosomal aberration test method using the rat peripheral blood lymphocyte; 3) taste disorder induced by zinc deficiency in rat and oxidative stress; 4) mutagenecity caused by hypertension; 5) zinc excess intake enhances the induction of micronuclei in rat bone marrow cells; 6) evaluation of mutagenic potential related to diabetes mellitus; 7) a work of the method for analysis of 8-hydroxydeoxyguanosine (8-OHdG) with gas chromatography/mass spectrometry (GC/MS); 8) evidence-based medicine (EBM); 9) cost-effectiveness of vaccination; 10) prevalence of menopausal symptoms; 11) associations between body weight, waist circumference, and cardiovascular risk factors; 12) long-term follow-up study in patients with type 2 diabetics; 13) pressure ulcer healing and zinc supplementation with polaprezinc; 14) questionnaire survey of professional divers; and 15) mental health in the workplace.

Research Activities

Experimental Medicine

1. Induction of micronuclei in human peripheral blood lymphocytes from workers exposed to indium tin oxide

Human peripheral blood lymphocytes derived from workers exposed to indium tin oxide were incubated for 48 hours in RPMI 1640 containing phytohemagglutinin. The cells were then cultured with cytochalasin B for an additional 48 hours. The frequency of micronuclei in each worker was 0.7% to 1.7%.

2. Induction of chromosome aberration in human peripheral blood lymphocytes from workers exposed to indium tin oxide

Human peripheral blood lymphocytes from workers exposed to indium tin oxide were incubated for 48 hours in RPMI 1640 containing phytohemagglutinin. The result showed no chromosome aberration attributable to exposure to indium tin oxide.

3. Examination of the chromosomal aberration test method using rat peripheral blood lymphocytes

A study is in progress to establish optimal concentrations of several kinds of mitogen.

4. Taste disorder induced by zinc deficiency in rat and oxidative stress

Rats were fed a zinc-deficient diet with distilled water and hydrochloride quinine. Hydrochloride quinine intake increased in rats fed the zinc-deficient diet. The rats fed the zinc-deficient diet received injections of tempol. Hydrochloride quinine

intake did not decrease in rats fed the zinc-deficient diet. The induction of taste disorder in rats with zinc deficiency was not related to the active oxygen species.

5. Mutagenecity caused by hypertension

Hypertension is a lifestyle-related disease in which increased oxidative stress can be excessive, suggesting that cancer risk increases with oxidative DNA damage. The *in vivo* micronucleus test was performed with hypertensive rats aged 28 to 40 weeks. Damage to DNA tended to increase with each passing micronuclei induction. In the future, we will evaluate 8-OHdG.

6. Excess zinc intake enhances the induction of micronuclei in rat bone marrow cells

Zinc is an essential trace element that works as an active center of approximately 300 enzymes to maintain cellular functions. Recently, zinc can be administered with diet supplements and other preparations. However, many people do not abide the adequate dosage by a wrong idea, the promotion of health or more by taking zinc and many supplements. Moreover, zinc toxicity is not widely known. Therefore, we examined mutagenicity due to zinc.

7. Evaluation of mutagenic potential related to diabetes mellitus

Effect of streptozotocin-induced diabetes mellitus on micronucleus formation in rats was studied with the in *vivo* micronucleus assay. Diseased animal was killed at 4, 7, 10, and 14 weeks after induction of diabetes mellitus. A tendency for the micronucleus frequency to increase was observed, but this difference was not significant. A more sensitive method is required to confirm this result.

8. A work of the method for analysis of 8-OHdG by GC/MS

The variable that best indicates the oxidation damage of DNA is 8-OHdG. For this reason, the measurement of 8-OHdG with GC/MS was investigated.

Epidemiology, EBM, investigation, and medical informatics

1. EBM

A systematized body of epidemiologic principles with which studies can be designed and judged has been established only in the last two decades. These principles have evolved in tandem with an explosion of epidemiologic activity covering a wide range of health problems. Our greatest concern is to clarify risk factors for adult disease and intractable diseases. We also studied the methodology of medical informatics education and EBM.

2. Cost-effectiveness of vaccination

We established a standard method to analyze the cost-effectiveness of vaccination and assessed the cost-effectiveness of implementing routine vaccination programs in Japan: 6 vaccines for children (*Haemophilus influenzae* type b, pneumococcal conjugate vaccine 7, varicella, mumps, hepatitis B virus, and human papilloma virus) and 1 vaccine for adults (pneumococcal conjugate vaccine 23).

3. Prevalence of menopausal symptoms

Questionnaire surveys on menopausal symptoms were administered to 50- and 60-year-old women who lived in northern Kawasaki. We determined the prevalence of awareness about menopause and symptoms in community-dwelling Japanese women.

4. Associations between body weight, waist circumference, and cardiovascular risk factors

Using annual health examination data, we examined the associations between body weight, waist circumference, and cardiovascular risk factors in Japanese male workers.

5. Long-term follow-up study in type 2 diabetics

Fasting plasma glucose (FPG) variability was a risk factor for nonproliferative and proliferative diabetic retinopathy independent of the mean FPG or HbA1c in patients with type 2 diabetes. The development of proliferative diabetic retinopathy was also significantly associated with mean HbA1c more than 5 years earlier and with mean FPG more than 10 years earlier.

6. Pressure ulcer healing and zinc supplementation with polaprezinc

We performed a nonrandomized controlled clinical trial to examine the effects of the zinc-containing preparation polaprezinc on the healing of chronic pressure ulcers. The results of this trial suggest that polaprezinc is beneficial for the treatment of pressure ulcers.

7. Questionnaire survey for professional divers

The occupational health of the professional harbor divers was analyzed by means of a questionnaire survey with regard to the operations management and prevention of dysbarism. There were many problems with recompression therapy for diver's disease based on the Industrial Safety and Health Act.

8. Mental health in the workplace

Mental health in the workplace is increasingly recognized as a serious problem. There are some questionnaires to prevent mental disease in Japan. A concrete question in these questionnaires is the importance of managing stress in the workplace. The purpose of this study was to investigate stress in the workplace with a new questionnaire.

Publications

Miyazaki T, Takenaka T, Inoue T, Sato M, Hanyu M, Eiki Y, Nodera M, Yanagisawa H, Ohno Y, Shibasaki S, Suzuki H. Klotho expression is induced by calorie restriction in adult male rats. *Trace Nutrients Res* 2010; **27:** 92–6.

Iwase T, Uehara Y, Shinji H, Tajima A, Seo H, Takada K, Agata T, Mizunoe Y. Staphylococcus epidermidis Esp inhibits Staphylococcus aureus biofilm formation and nasal colonization. *Nature* 2010; **465:** 346–9.

Suka M, Miwa Y, Ono Y, Yanagisawa H. BMI, waist circumference, and clustering of cardiovascular risk factors in Japanese adults. *Environ Health Prev Med* 2011; **16:** 90–6.

Takao T, Ide T, Yanagisawa H, Kikuchi M, Kawazu S, Matsuyama Y. The effect of fasting plasma glucose variability on the risk of retinopathy in type 2 diabetic patients: retrospective long-term follow-up. *Diabetes Res Clin Pract* 2010; **89:** 296-302.

Reviews and Books

Takagi R, Suzuki Y, Seki Y, Ikehata M, Kajihara C, Shimizu H, Yanagisawa H. Indium chloride-induced micronuclei in in vivo and in vitro experimental systems. *J Occup Health* 2011; **53:** 102–9.