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*Meeting Report*

# The Twentieth International Symposium of the Sapporo Cancer Seminar Foundation: Gene Environment Interaction and Cancer Prevention[1]

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## Abstract

**The main goal of this Symposium was to discuss new information that could be used for the development of effective and novel approaches in cancer prevention. Mounting evidence indicates that genetic predisposition to cancer plays an important role in the etiology of the disease and that multistage carcinogenesis is for the most part based on multiple genetic changes, favoring cell survival. It is also evident that a variety of environmental factors lead to carcinogenic changes and determine cancer-causative or cancer-facilitative genetic changes; these factors may be endogenous in origin, as for example those that are endocrinologic in nature, or may come from the external environment, as for example products in tobacco smoke or in industrial pollution. It is therefore obvious that gene-environment interactions play a pivotal role in carcinogenesis and consequently may offer specific sites of intervention that may be useful for the development of cancer prevention. In general, cancer prevention can be implemented through Public Health measures, as is typically the case for intervention on smoking, industrial pollution, aflatoxin B contamination or, when we know more about it, dietary habits. On the other hand, it should become possible to design more rational chemoprevention and immunoprevention trials as more becomes known about the genetic changes predisposing to cancer and about the gene products that are responsible for the phenotypic changes leading to neoplasia.**

## Introduction

At this Symposium, important issues were discussed and questions raised related to the interactions of gene function and both "endogenous" and "exogenous" environmental factors and related to their roles in the development of cancer. Several types of mostly epithelial cancers were considered. The influence of DNA repair on carcinogenesis, interindividual and interspecies differences, mechanisms of prevention of skin cancer as a well-studied model, cancer cell motility as a determinant of progression, and immunological functions of relevance to surveillance were all discussed. Specific contributions are briefly outlined below.

## Triggering Carcinogenesis

In his keynote address, Dr. T. Sugimura pointed out the occupational and dietary factors as well as cigarette smoke components that are clearly instrumental in triggering carcinogenesis together with the genetic factors predisposing to it. Several molecular mechanisms specifically proven to be instrumental in the action of certain carcinogens were reviewed, and the importance of carcinogen activation *versus* catabolism was emphasized. The role of DNA methylation at CpG sites in genomic instability was discussed as one of the phenomena of relevance, as was the mechanisms of cocarcinogenic action of such environmental agents as teleocidin B, phorbol ester (TPA[3]) which activate PKC, or okadaic acid, which inhibits protein phosphatase. The influence of viral or bacterial infections was also examined. The whole address was ultimately focused on the fundamental question as to why some individuals exposed to carcinogens, for example smokers, do not develop cancer, and others do. What are the genetic factors and related molecular mechanisms predisposing to neoplastic transformation?

## Specific Diseases

Extensive discussions were focused on breast, colon, lung, and primary liver cancers.

**Breast Cancer.** Dr. Narod provided convincing evidence that mutations of *BCRA1* and *BCRA2* have a predisposing role in breast cancer. The cofactors involved can be hormones of endogenous origin or administered exogenously for replacement therapy or contraceptives. Other exogenous cofactors are derived from smoking, overconsumption of alcohol, dietary factors, X-irradiation, and other known carcinogens. The mutations in the *BCRA1* and *BCRA2* genes have relatively low frequency but high penetrance; this results in a high lifetime risk. Factors influencing DNA repair, carcinogen and hormone metabolism, and cytochrome P-450 functions also affect the incidence of the disease. Differences between *BCRA1* and *BCRA2* are known but not always understood; for example, it is not known why breastfeeding has a positive effect on *BCRA1* but does not affect *BCRA2*. The important role of endogenous endocrinological factors is also indicated by the fact that in *BCRA1* mutation carriers, pregnancy increases the risk and early oophorectomy decreases the risk. Interestingly, smoking decreases the risk by virtue of its antiestrogenic effects. Oral contraceptives decrease the risk of ovarian cancer but increase that of breast cancer. This is an additional observation pointing at the complexities of the interactions of endocrinological factors with individual genetic characteristics. Given the fact that mammary cells in *BCRA1*-positive individuals are usually estrogen receptor-negative and that Tamoxifen has no effect on estrogen receptor-negative cells, it is surprising that the 40% risk of second contralateral breast cancer in survivors from first breast cancer is decreased to 6% in patients treated with Tamoxifen for at least 4 years.

**Colon Cancer.** Three presentations concerned colon cancer. Dr. Shimizu focused on a discussion of genetic and environmental factors

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[1] This Symposium was held July 4–7, 2000 in Sapporo, Hokkaido, Japan and was chaired by Dr. Hiroshi Kobayashi, Director General of the Sapporo Cancer Seminar Foundation.

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[3] The abbreviations used are: TPA, 12-*o*-tetradecanoyl phorbol-13-acetate; PKC, protein kinase C; NAT, *N*-acetyltransferase; GST, glutathione *S*-transferase; ROS, reactive oxygen species; COX, cyclooxygenase; IL, interleukin; HBV, hepatitis B virus; AFB1, aflatoxin $B_1$; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine; CBI, covalent binding index; NF-$\kappa$B, nuclear factor-$\kappa$B; PTK, protein tyrosine kinase; HTLV, human T-cell leukemia virus; ATL, adult T-cell leukemia; HAM/TSP, HTLV-associated myelopathy/tropical sporadic paraparesis; NK, natural killer; AOM, azoxymethane.

and their interactions affecting the incidence of colon cancer. The possible effects of diet as related to differences in colon cancer incidence between Japanese in Japan and Japanese in California were considered, as were differences related to tumor onset in different parts of the color. The possible influence of phenotypic factors related to, for example, physical activity, were discussed. Genetic factors were reflected not only in immigrants from Japan but also in first-generation immigrants born in the United States. Not only the incidence of colon cancer, which is low in Japan, equalized that in non-Japanese Americans among immigrants of young age, but some "overshoot" occurred, for example in sigmoid cancer, among immigrants as well as in first-generation immigrants born in the United States. Dietary factors possibly related to these differences as well as genetic factors were considered. The *NAT-2* genotype, or *NAT-1,* showed no interaction. Some effects of red meat consumption as a factor affecting colon cancer incidence among Japanese immigrants in the United States was suggested, but many questions about this association remain to be answered.

Dr. Hill reviewed the histopathology and molecular biology of colon cancer in the light of the changes demonstrated by Vogelstein and his group to occur in association with progression toward, and of, colon neoplasias. He pointed out that progression from adenoma to cancer is associated with the adenomatous polyposis coli cascade of mutations in 80% of the cases, and the replication error pathway-related microsatellite instability occurs in 20% of familial polyposis cases but in ~70% or more of hereditary nonpolyposis colorectal carcinoma cases. Slow and fast isoforms of *NAT-2* were associated with different rates of risk after red meat consumption. Polymorphism in other enzymes, such as GSTs and the folate system, may be, to some extent, risk modifiers.

Dr. Bartsch discussed the molecular pathways leading to the development of colon cancer, as affected by mutations, hypermethylation, and enzyme polymorphism related to drug or folate metabolism. Oxidative stress is prominent in causing mutations of genes related to cancer. Ulcerative colitis and other inflammatory bowel diseases are factors predisposing to colon cancer. Chronic inflammation in these diseases leads to overproduction of ROS. In familial adenomatous polyposis, an autosomal dominant disease, COX-2 overexpression determines increased oxidative arachidonic acid metabolism and through a multistep process also in this case, ROS are generated. Etheno DNA adducts derive from reactive aldhydes generated during lipid peroxidation and are also a consequence of nitric oxide overproduction. They occur in addition to direct oxidative DNA base damage. For the first time increased DNA etheno adducts were demonstrated in familial adenomatous polyposis patients and more so in those with inflammatory bowel diseases in comparison with normal tissues. These adducts are promutagenic and increase genetic instability and thus represent useful biomarkers. Nitric oxide generated as a consequence of stimulation by IL-I$\beta$, IFN-$\gamma$, or tumor necrosis factor-$\alpha$ also markedly decreased global DNA repair processes. Various new antioxidants were found in extravirgin olive oil, which may protect against colon cancer as well as cardiovascular diseases by reducing ROS formation; these antioxidants are present in lesser quantities in refined oils and not at all in seed oils.

**Lung Cancer.** Five presentations concerned lung cancer. Dr. Yang discussed the participation of genetic *versus* environmental factors in the etiology of the disease. The lung cancer incidence appears to be greater in light smokers than in heavy smokers, who show only a 10% incidence. The reasons for this surprising difference have not yet been clarified. In smokers, squamous cell carcinomas prevail, whereas in nonsmokers, adenocarcinomas are more frequent. Chronic obstructive pulmonary disease is a predisposing factor that is in part related to $\alpha_1$-antitrypsin deficiency. This genetically determined syndrome is common among Caucasians from Europe; $\alpha_1$-antitrypsin neutralizes neutrophil elastase, which destroys lung tissues and leads to the development of emphesema. Smoking exacerbates further the $\alpha_1$-antitrypsin deficiency syndrome, and 10–30% of lung cancer can be attributed to the interactions between smoking and this genetically determined syndrome. Another example of gene modifiers is represented by resistance to drugs that is, at least in part, responsible for failure in lung cancer treatment. The therapeutic effects of cisplatin or cyclophosphamide can be modified by genetically determined deficiency of glutathione and glutathione-dependent enzymes. In a study, 241 patients with small cell and non-small cell lung cancer were considered together and grouped into early and late stages. Each patient was genotyped for *GSTM1, GSTT1* [allele types defined as null (N) or positive (P)], and for *GSTP1* and $\gamma$-*GCS* [defined as low (L) or high (H)]. Among nonsmokers, the 1-year survival rate was 63–83% for patients with *PP*/*PH* genotypes compared with 92–100% for patients in the other groups.

Dr. Takahashi pointed out that among the genetic lesions associated with lung cancer, the most frequent was P53 mutational inactivation. These mutations occurred in 80–90% of small cell lung cancer and in ~70% of non-small cell lung cancer, indicating differences in this respect among lung cancer subtypes. Increases of the P53 mutations are associated with lifetime smoking and are represented by a GC-TA transversion that occurs infrequently in the absence of exogenous carcinogens. Additional studies indicated that the initiation and maintenance of the smoking habit also involve hereditary factors. Nicotine binds to a specific receptor in mid-brain that is genetically determined, and this binding leads to increases in dopamine release. Dopamine provides for reward and reinforcement behaviors. The *DRD2* gene encodes the dopamine receptor, and the *DRD2 A2*/*A2* genotype has a 3-fold higher risk of acquiring the smoking habit in the Japanese population. Ethnic differences in genotype/phenotype associations were noted in this respect.

Dr. Cheng stressed the importance of using suitable models to study the molecular changes occurring during lung cancer progression. His group established four SV40 immortalized human bronchial epithelial cell lines that showed changes suggestive of malignancy but did not grow into tumors when transplanted into nude mice and may represent a model for premalignant lesions. This type of model may be useful in studies of progression and regression and specifically to identify genetic elements determining the reversability or irreversability of the neoplastic development process.

Dr. Yokota discussed the role of DNA repair in preventing the fixing of mutational lesions, with emphasis on the etiology of lung cancer. He focused on the mutagenic base lesions in DNA caused by ROS, such as 8-oxo-guanine; GC-TA transversion occurs unless repair is carried out before cell division. A human homologue of the yeast enzyme *OGGI* (*hOGGI*) appears to be the major repair enzyme involved and is mapped on the short arm of chromosome 3, which is frequently deleted in cancer. Human *OGGI* specifically binds to 8-oxo-guanine in DNA and has glycosylase/AP lyase activity instrumental in excision repair of this lesion. Three major types of transcripts of the *OGGI* gene were identified, with one binding to nuclear DNA motifs and the other binding to mitochondrial DNA. The repair activity was greater in OGGI-Ser-326 protein that in an *Escherichia coli* strain; in Okinawa, male individuals with the *Cys*/*Cys* genotype had a 3-fold higher risk of squamous cell carcinoma than people with the *Ser*/*Cys* or *Ser*/*Ser* genotype, after adjusting for age and smoking history. The risk increase was more evident among heavy smokers. As shown in OGGI-knockout mice, alternative repair pathways seem to exist.

Dr. H. Sugimura explored the polymorphism existing among genes coding for carcinogen detoxification and activation enzymes and

indicated its role in determining individual genetic differences in susceptibility to lung and stomach cancers. Carcinogenesis risk-determining genes such as *CYP1A1, CYP2E1, GSTMI,* and *OGGI* were evaluated for polymorphism in case-control studies, including consideration of smoking and dietary factors, and comparison were made between Okinawa and Sao Paulo populations as well as Australia, Europe, and China populations. Differences were seen in specific mutations in different populations, and some of these correlated with differences in risk for cancer. In the case of gastric cancer, cytokines such as IL-8, IL-I$\beta$, or tumor necrosis factor-$\alpha$ can affect the presence of free radicals or gastric acid, and in turn these effects are influenced by polymorphism of the related genes. Thus far, very few studies have been carefully carried out on the relationship between dietary factors and polymorphism of relevant risk-affecting genes.

**Liver Cancer.** Two presentations focused on liver cancer. Dr. Montesano discussed the etiological role of HBV and dietary factors, primarily AFB1, in the development of primary liver cancer, particularly in Gambia, West Africa; the relative contribution of these two factors to the risk of developing hepatocellular carcinoma and their interactions are still poorly understood. A careful study is being conducted on the protective effects of vaccination against HBV; AFB1 exposure is being measured by the presence of AFB1-albumin adducts in blood and of a specific GC-TA transversion mutation in codon 249 of the *p53* gene (Ser-249) in hepatocellular carcinoma. This mutation in plasma DNA corresponded well to that in tumor DNA, and this facilitated correlative studies. The presence of AFB1 in uterus had also been indicated. Synergistic interactions between HBV and AFB1 in hepatocarcinogenesis were demonstrated. The occurrence of differences in mutations among different parts of the world and correlations with differences in hepatocarcinogenesis all are compatible with the etiological role of AFB1. Vaccination against HBV was found to be effective in the prevention of infection and the establishment of carriers.

Dr. Kensler reported on studies of hepatocarcinogenesis, where preventive factors affecting tumor development are being considered. The induction of phase 2 enzymes, such as glutathione-*S*-transferases (GST), UDP-glucuronyl transferases, and quinone reductases, represents one of the main mechanisms of protection against the carcinogenic, mutational, and toxic effects of certain carcinogens through their catabolic inactivation. Induction of these enzymes can be obtained by the administration of several naturally occurring and synthetic chemopreventive agents to include 1,2-dithiole-3-thiones and sulforaphane. Oltipraz, a substituted 1,2-dithiole-3-thione, was originally used as an antischistosomal agent but has now been shown to act as a chemopreventive agent against different classes of carcinogens targeting a number of different human tissues. In rodents, Oltipraz was found to prevent AFB1-induced hepatocarcinogenesis, indicating that increased expression of genes coding for phase 2 enzymes has preventive importance through inhibition of AFB1; activation by phase 1 enzymes may also be effective. In fact, decrease of CypIAI, of the excretion of the oxidative anabolites of AFB1 and AFM1, and of DNA adduct formation are also related to a decrease in carcinogenesis by AFB1. Exposure of rodents to Oltipraz and related compounds induces the nuclear accumulation of the transcription factor Nrf2 with increased binding to antioxidant response element. This induction leads to the transcriptional activation of ~20 genes coding enzymes involved in carcinogen detoxification and to the attenuation of oxidative stress; this induction does not occur in Nrf2-deficient mice. In the Qidong peninsula in northeast China, a placebo-controlled double blind clinical study of Oltipraz is being carried out with 240 participants. Residents in this area are exposed to AFB1 and are at high risk to develop liver cancer. When Oltipraz was given orally for 8 weeks, at the dose of 125 mg daily, the urinary excretion of AFB-mercapturic acid conjugate was greatly increased; at the dose of 500 mg once a week, a significant reduction for AFM1 was seen. AFB1-albumin adducts were also measured. This study indicated the feasability of inducing effective phase 2 enzyme actions in humans and is being followed by an ongoing longer term intervention study aimed at reducing liver cancer risk through alteration in AFB1 metabolism.

## Modifiers of Carcinogenesis

Several processes capable of modifying carcinogenic risk, from both the endogenous and exogenous environment, were discussed in seven presentations.

Dr. Garner addressed the question of whether animal carcinogens are also carcinogenic to humans. Comparative studies of carcinogen activation and metabolism were carried out using an ultrasensitive analytical technique based on accelerator mass spectrometry. The accelerator mass spectrometry methodology can analyze attomole to zeptomole quantities, *e.g.,* of $^{14}$C-labeled carcinogen metabolites and adducts. These were examined for AFB1 and AFB2, pyrene, benzo(*a*)pyrene the heterocyclic amine MeIQx, PhIP, and methylurea plus nitrite or nitrate. PhIP is activated through the sequential action of CYPIA2 and NAT2, and its *O*-acetyl derivative can form DNA adducts. After the administration of minute doses of radio-labeled carcinogens, and using the CBI as a measure of DNA adduct formation, it was possible to compare CBIs in human colon with those in rat. In humans, the order of CBIs was BP > PhIP > AFB1 > pyrene > MelQx > PhIP > AFB2. In rats, it was AFB1 > BP > pyrene > MeIQx > PhIP > AFB2. No correlations were found between AFB1-albumin and AFB1-DNA adducts. These studies showed for the first time how humans metabolize a number of carcinogens at low doses as compared with rodents. Also, it was concluded that the rat is not fully representative of humans in terms of DNA adduct formation by the various carcinogens studied.

Dr. Surh reported that naturally occuring phenolic substances, also present in edible and medicinal plants, have antioxidative and anti-inflammatory properties that contribute to their antimutagenic and anticarcinogenic actions. Inducible COX-2 and inducible nitric oxide synthase mediate inflammatory processes. Because inflammation is linked to tumor production, anti-inflammatory substances are expected to exert preventive effects on carcinogenesis. As an example, curcumin attenuates TPA-induced inflammation and skin tumor promotion in mice, reduces the TPA activation of ornithine decarboxylase, and reduces the expression of its mRNA. This effect appeared to be mediated through a reduced activation of NF-$\kappa$B. These effects were also caused by several other natural products such as Capsaicin, present in red pepper, or the ginsenoside Rg3. A possible mechanism for the reduced activation of NF-$\kappa$B would be a reduced degradation of the inhibitory unit I$\kappa$B. Some of these effects were also seen in cultured human promyelocytic leukemia cells.

Dr. Zanker discussed the migration of postmitotic leukocytes and of tumor cells within a three-dimensional collagen gel, whether or not stimulated by certain chemokines, which involve the action of PKC and of PTKs. The migration of these cells is induced by formylated methyl leucine phenylalamine and stopped by IL-8. Colon cancer cells require only PKC activity for spontaneous locomotion but catecholamine-induced motion is PTK dependent. PKC is localized in the leading cap of migrating leukocytes; actin and myosin are also present but not in a well-organized mode. Changes in calcium distribution between the endoplasmic reticulum and cytoplasm occur with motion, with calcium being released at the edge of moving cells. Focal adhesion kinase is phosphorylated in migrating cells, depending on conditions, and is also present at the leading edge of the cells. In

tumor cells, three functions affect migration: signalling through PTK receptor to PKC, integrin action, and the signalling through the seven-helix receptor for catecholamines to small G protein, protein kinases A, and RhoA. The increases of the latter induced migration. Indeed, colon cancer cells can be induced to migrate by epinephrine, and this effect is reduced by the protein kinase A inhibitor Rot. Cells transfected with small G protein and activated by epinephrine are induced to migrate. In comparing HER2/neu-negative and -positive breast cancer cells, it was found that PKC$\alpha$ was high in the negative cells and low in the positive cells; TPA induced migration of the cells with high PKC$\alpha$ but not in those with low PKC$\alpha$. Thus, clearly migration of normal as well as tumor cells is tightly regulated through different signals that originated from extracellular stimuli.

Dr. S. Sonoda discussed the epidemiology of human T cell leukemia virus type I (HTLV-I) and type II (HTLV-II) which cause ATL and related diseases such as the HAM/TSP. The virus is vertically transmitted through the mother's milk, but the disease occurs much later in life, after age 60, and only in 1 of 1000 infected individuals, most of whom are carriers. A comparative study was carried out in southern Japanese populations at risk for ATL and Afro-Caribbeans and South American Black with HLA alleles diversified into determinants of sensitivity or resistance. An analysis of HLA polymorphism was carried out also with reference to recognition of viral env and tax proteins and related to risk of ATL and HAM/TSP. The epidemiology of the polymorphism was related to the epidemiology of disease type. The overall results suggested that genetic diversity of HLA genes is naturally selected by HTLV-I/II, the infection foci of which will develop ATL and HAM/TSP.

Dr. Nakachi described the results of a prospective cohort study among the Japanese general population analyzing the association between levels of NK activity of peripheral blood lymphocytes and cancer incidence within an 11-year period. Within the 154 cases studied, medium to high levels of NK activity correlated with low cancer risk and low NK activity with high risk. Analysis of perforin *versus* granzyme mechanisms of NK action as well as of the presence of receptor on NK cells was also carried out. Significantly, NK activity was decreased among smokers. The overall results were consistent with the validity of the immunosurveillance hypothesis.

Dr. Zhang reviewed the current status and potential of gene therapy of cancer. Transfection with wild-type *p53* gene, transfection with suicidal genes such as *herpes simplex virus-thymidine kinase,* followed by treatment with prodrugs specifically activated by the viral thymidine kinase, are examples of current approaches. The difficulties inherent in targeting the genes to tumor cells were emphasized. Transfection *ex vivo* with cytokine genes of *B7-1* and *B7-2* genes was discussed. Viral vectors with TAA cDNA inserts or inserts coding sequences capable of binding relevant MHC class I molecules can provide useful vaccines after transfection of dendritic cells. Combined transfection with different cytokine genes can be very effective vaccines under certain experimental conditions. In some cases, transfer of tumor-derived RNA may provide vaccine based on multiple TAA expression. Should this approach be validated in careful experimentation, it may provide advantages related to, among others, the possibility of reducing tumor escape attributable to heterogeneity in TAA expression.

Dr. Turusov discussed the effects of sex hormones given during pregnancy as related to the time of administration. Occurrence of androgen-dependent tumors and hyperandrogenization were observed in adult life of progeny exposed to sex hormones after male sex differentiation had started; likewise estrogen-dependent tumors occurred in female progeny exposed to sex hormones after female sex differentiation had started. The administration of diethylstilbestrol during pregnancy induces tumors in first-generation progeny and, in some rare cases, apparently also in the second generation. These studies provide an example of transplacental carcinogenesis.

## Poster Presentations

In addition to the presentations summarized above, 12 short communications were presented and outlined in related posters. These are very briefly summarized below.

Dr. Ariyoshi discussed the association of lung cancer with the specific CYP2A6 subtype of P-450, which is a determinant of the metabolic activation of tobacco-related nitrosamines to carcinogenic forms. Polymorphism in this gene is correlated with incidence of tobacco-related lung cancer.

Dr. Seon-Hee Oh studied the mechanism of apoptosis during cholestasis in the rat after bile duct ligation. Increases in Fas expression and changes in Bcl 2 and Bax were noted that were associated with c-Myc expression. Additional parameters are under study.

Dr. Sang-Jun Lee described the effects of a ginseng-derived saponin on inhibiting proliferation and inducing apoptosis of HL60 cells. The marked apoptotic effect appeared mediated through inducing activation of caspase-3 protease via mitochondrial cytochrome *c* release.

Dr. Hamajima described the effect of polymorphism of the gene expressing catechol-*O*-methytransferase on breast cancer risk in Japan; it was concluded that this polymorphism had a limited influence on breast cancer risk in Japan, in contrast with the findings by others in Taiwan.

Dr. Matsuo described the relationship between polymorphism of the gene of methylenetetrahydrofolate reductase and life style (smoking, alcohol consumption, and other factors) in affecting the incidence of malignant lymphoma. It was concluded that folate metabolism plays an important role in the occurrence of malignant lymphoma but does not interact with the life style factors examined.

Dr. Matsunaga discussed the effects of neonatal injection of protein-bound polysaccharide (PSK) or of small doses of AOM on the development of precancerous aberrant crypt foci in the rat intestine after the administration of higher doses of AOM at 7 weeks of age. The reduction of aberrant crypt foci seen after neonatal PSK was thymus dependent; that seen after AOM appeared to be related to the induction of drug-metabolizing enzymes.

Dr. Dashwood showed that in rats, chlorophyllin and indole-3-carbinol promoted colon tumors induced by dimethylhydrazine; these tumors contained specific forms of $\beta$-catenin mutants similar to those present in human cancer.

Dr. Okada discussed ROS as microenvironment factors inducing tumor progression. Using weakly metastatic fibrosarcoma (QR) cells, tumor progression was enhanced by coimplantation with inflammation inducing gelatin sponge; this effect was inhibited by the elimination of neutrophils from the tumor site. Increased levels of manganese superoxide dismutase and of 8-hydroxydeoxyguanosine correlating with ROS coincided with tumor progression.

Dr. Lee showed that rat strain-specific increases in susceptibility to dioxin (TCDD) toxicity correlated with decreased levels of GST and CYP17A and increases in CYPIA2 and II E-1, as determined by microarray.

Dr. Cornain described the epidemiology of skin cancer in Indonesia as related to sun/ultraviolet exposure, in addition to other risk factors. Ultraviolet-specific mutations of p53 were noted. Higher risks were associated with low educational level, daily work outdoors, and the wearing of short sleeves instead of long sleeves. High consumption of meat, eggs, fruits, and vegetables had protective effects.

Dr. Surh discussed the effects of naturally occurring diarylheptanoids on phorbol ester-stimulated COX-2 expression and NF-$\kappa$B

activation in cultured human MCF10A breast cells. In these cells, TPA induced COX-2 mRNA and COX-2 protein expressions in a time- and concentration-dependent manner. Inhibition of NF-κB suppressed this effect. Hirsutanone and curcumin reduced NF-κB stimulation by TPA consequent to inhibition of degradation of IκB.

Dr. Deng studied the effects of polymorphism in the *GSTM1* and *CYP1A1* genes on variation of susceptibility to lung cancer and found that *GSTM1* (−) and the *CYP1A1* exon 7 *Val*/*Val* genotype may be related to the risk of developing lung squamous cell carcinoma in Chinese populations.

## Conclusion

In conclusion, this conference emphasized the fact that genetic predisposition to cancer can be modified in either direction by factors derived from both the endogenous and the exogenous environments. The clarification of these interactions and of the mechanisms on which they are based should provide a basis for the development of effective approaches to the prevention of cancer.

## Appendix

The Program Committee consisted of Drs. Hiroshi Kobayashi (Sapporo Cancer Seminar Foundation, Japan), chairman; Fred F. Kadlubar (National Center for Toxicological Research, USA); Tomoyuki Kitagawa (JFCR Cancer Institute, Japan); Enrico Mihich (Roswell Park Cancer Institute, USA); and Suketami Tominaga (Aichi Cancer Center, Japan).

In addition to the Program Committee members, invited participants included: Helmut Bartsch (German Cancer Research Center, Germany); Shu-jun Cheng (Peking Union Medical College, China); R. Colin Garner (University of York, United Kingdom); Michael J. Hill (Lady Sobell GI Unit, Wexham Park Hospital, United Kingdom); Thomas Kensler (Johns Hopkins School of Hygiene, USA); Toshio Kuroki (Molecular Oncology Research Center, Showa University, Japan); Insu P. Lee (Korea Food and Drug Administration, National Institute of Toxicology Research, Korea); Ruggero Montesano (International Agency for Research on Cancer, France); Kei Nakachi (Saitama Cancer Center Research Institute, Japan); Steven Narod (Center for Research in Women's Health, University of Toronto, Ontario, Canada); Hiroyuki Shimizu (Gifu University School of Medicine, Japan); Shunro Sonoda (Department of Virology, Faculty of Medicine Kagoshima University, Japan); Haruhiko Sugimura (School of Medicine, Hamamatsu University, Japan); Takashi Sugimura (National Cancer Center, Japan); Young-Joon Surh (College of Pharmacy, Seoul National University, Korea); Takashi Takahashi (Laboratory of Ultrastructure Research, Aichi Cancer Center Research Institute, Japan); Vladimir Turusov (Laboratory of Carcinogenic Substances, All Union Cancer Research Center, Russia); Ping Yang (Mayo Foundation, USA); Jun Yokota (National Cancer Center Research Institute, Japan); Kurt Zanker (Institute for Immunology, University of Witten/Herdecke, Germany); and You hui Zhang (Cancer Institute, Peking Union Medical College, China).

The Posters were presented by: Noritaka Ariyoshi (Sapporo); S. Cornain (Jakarta); Rod Dashwood (Corvallis, USA); Yifu Deng (Nagoya); Noboyuki Hamajima (Nagoya); Y J Surh (Seoul); Insu P Lee (Seoul); Sang-jun Lee (Iksan, Korea); Kenichi Matsunaga (Tokyo); Keitaro Matsuo (Nagoya); Seon-Hee Oh (Iksan, Korea); and Futoshi Okada (Sapporo).