Meeting Report

Seventh Annual Sapporo Cancer Seminar

Primary and Secondary Prevention of Cancer[1]

This meeting focused on two subjects: (a) development of mass screening techniques for cancer and evaluation of secondary prevention; and (b) risk factors and ways of primary prevention of cancer. The organizing committee was chaired by K. Aoki (Nagoya University, Nagoya, Japan) and included A. S. Morrison (Brown University, Providence, RI), M. Hakama (University of Tampere, Tampere, Finland), K. Tamura (Hokkaido Cancer Society, Sapporo, Japan), H. Miyake (Sapporo Medical College, Sapporo, Japan), K. Saito (Hokkaido University, Sapporo, Japan), and H. Kobayashi (Hokkaido University, Sapporo, Japan).

The first half of the meeting was devoted to the secondary prevention of cancer. Morrison gave a lecture on methods of deriving information used in the formulation of cancer-screening policy. The best method of evaluating a policy is an experimental study, but serious practical difficulties restrict their use. Nonexperimental methods have inherent design limitations for comparing policy options. Two types of models that may be helpful in the formulation of policy are exposure-response curves, which depict functional relationships between quantitative aspects of screening policy (e.g., frequency) and the reduction in mortality that is achieved, and intermediate-outcome models, which enable the sizes of reductions in mortality to be predicted from changes in characteristics of disease (e.g., stage) at detection as brought about by a particular screening policy.

Most subsequent presentations concerned new screening techniques, the evaluation of screening, or screening policy in Japan.

New Techniques

S. Kobayashi (Aichi Cancer Center Hospital, Nagoya, Japan) described an immunological method of testing for fecal blood. The test was developed in order to remedy deficiencies in the Hemoccult test, and the new test appears to result in a relatively high predictive value. Compared to the Hemoccult test, the immunological test is complex and expensive so that the usefulness of the test in mass screening is uncertain.

S. Ikeda (National Cancer Center Hospital, Tokyo, Japan) described two developments in screening for lung cancer. The first is digitalized processing and storage of chest X-rays. Ikeda emphasized that the necessary equipment is expensive and large. The second development is a method of bronchoscopy in which a tiny television camera is mounted in the tip of the bronchoscope.

C. Kido (Aichi Cancer Center Hospital, Nagoya, Japan) described a method of mammography that displays the images on a monitor by use of an image processor. The method has a number of advantages with respect to conventional mammography: very small tumors can be detected; one view (lateral) is sufficient; the method is inexpensive; the dose of radiation is very low; examinations are rapid and easily accomplished; and the training of technicians is simplified.

H. Watanabe (Kyoto Prefectural University of Medicine, Kyoto, Japan) reported on screening for carcinoma of the prostate by use of transrectal sonography. The technique has been adapted for use in a mobile van. The capacity of the van units is 20 examinations per hour, or 150 per day.

T. Takeda (Sapporo National Hospital, Sapporo, Japan) discussed screening for neuroblastoma. The question of screening for childhood cancer has received relatively little attention. The method used by Takeda involves measurement of urinary vanillylmandelic acid and homovanillic acid by use of liquid chromatography in 6-month-old infants.

Evaluation

Results were reported from several studies of the relation of screening to cancer mortality. R. S. Fontana (Mayo Clinic, Rochester, MN) presented recent results of an experimental study of screening for lung cancer. Male smokers who did not have detectable lung cancer at entry were randomized to an intensively screened group ($n = 4618$) or a control group ($n = 4593$). The screened group was urged to have chest X-ray and sputum cytology examinations every 4 months. The distribution of extent of disease at diagnosis and the survival of cases were more favorable in the screened group than in the control group. An intriguing finding is that the 84-month cumulative incidence of lung cancer was higher in the screened group (206 cases) than in the control group (122 cases). After 11 years, however, the numbers of lung cancer deaths were nearly equal, with 122 in the screened group and 115 in the control group. Other experimental studies of screening for lung cancer in the United States also have found little or no reduction in lung cancer mortality attributable to screening.

Hakama presented data on screening for cervical cancer in Finland. His analysis was based on cervical cancer mortality by time and age in relation to screening activities. He reported positive results similar to those from other parts of Europe and from North America. Thus, the available data generally support the value of screening for cervical cancer.

F. deWaard (National Institute of Public Health and Environmental Hygiene, Bilthoven, The Netherlands) presented the results of a case-control study of screening for breast cancer (by clinical examination and mammography) in women who were at least 50 years of age, in an area with an ongoing screening program. The cases consisted of 46 women who died of breast cancer after the program began. The controls were 138 women living in the study area at the times that the corresponding breast cancer patients died. It was determined whether each case and control had accepted the invitation to be screened. The protective relationship that was observed between screening and breast cancer mortality is somewhat stronger than has been observed in other studies. Taken as a group, however, the results of both experimental and nonexperimental studies of screening for breast cancer are positive and consistent.

The efficacy of screening for stomach cancer was investigated nonexperimentally by S. Hisamichi (Tohoku University, Sendai, Japan) and A. Oshima (Osaka Clinic for Detection and

Prevention of Cancer, Osaka, Japan). On the basis of data from Miyagi prefecture, Hisamichi reported that mortality from stomach cancer in Japan has been decreasing during the past 2 decades. The decline in mortality has been greatest in those age groups that have been screened most intensively. Hisamichi also reported the results of a follow-up study in which the stomach cancer mortality of screened persons was only about one-half that of unscreened persons. Oshima presented results of a case-control study of screening for stomach cancer in Nose Town, Osaka. Again, the stomach cancer death rate was about one-half as high in screened as in unscreened persons. Thus, the available data on the efficacy of screening for stomach cancer are positive and consistent.

H. Yanagawa (Jichi Medical School, Tochigi, Japan) described the use of a simulation model of the efficacy of screening for cervical cancer. The model is based on a Markov chain that includes elements related to case-finding and treatment. Screening increases the number of early-stage cases and decreases both the number of late-stage cases and the mortality rate from cervical cancer. Data on the natural history of cervical cancer are needed to strengthen the model and to aid in the planning and evaluation of screening programs.

Another aspect of screening is its operational features. The predictive value, *i.e.*, the proportion of people with confirmed cancer among all positive screenees, is a useful measure. The predictive value depends strongly on the prevalence of the detectable preclinical phase of the disease in screenees and on the specificity of the test that is used.

S. Tominaga (Aichi Cancer Center Research Institute, Nagoya, Japan) presented data related to the predictive value of screening for breast cancer in Japan. Of the women screened, 4.2% had positive tests, and the prevalence of cancer detected was 0.69 per 1000. In the discussion of this paper, it was pointed out that these data suggest a predictive value of about 1.6%. An important reason for the low predictive value is the low prevalence of the disease.

Oshima indicated that the predictive value in screening for stomach cancer is about 1% for the program with which he is involved. This low number is related to the low specificity (about 85%) of testing.

In screening for prostatic cancer as described by Watanabe, 25 confirmed cases were detected in 1521 men who had positive tests. The predictive value of testing was addressed during the discussion period. These data indicate that the predictive value is 1.6%. Reasons for the low predictive value are the low prevalence of prostatic cancer in Japan (about 0.5 per 1000 in the program reported) and the low specificy of testing. Of 5213 men screened, 1521 tested positive, which was, in large part, a consequence of the high frequency of benign prostatic hypertrophy.

In screening infants for neuroblastoma (as described by Takeda), 1.1% of 90,000 infants tested had positive initial tests and were retested. On the basis of retesting, 0.08% were recommended for clinical examinations and 17 cases were confirmed. In discussion of this report, it was pointed out that the predictive value depended strongly on the definition of a positive test. If retesting was the definition, the predictive value was 1.7%. If an examination was considered positive only if the retest was positive, the predictive value was 24%.

Screening Policy

Tamura reported that mass screening for stomach cancer began around 1960 in Japan. The methods of detection used are double-contrast X-ray and endoscopy. Nationwide, 5.1 million persons are screened each year for stomach cancer. The Hokkaido Cancer Society began a stomach cancer screening program in 1963; a total of 2.5 million persons were examined in this program as of 1985. In men, the detected prevalence at the initial examination was 364.8 per million; at subsequent examinations the prevalence was 135.5 per million. The cancers detected tend to be at an early stage and to have a favorable prognosis.

M. Aoki (Research Institute of Tuberculosis, Tokyo, Japan) and Ikeda reported on the policy of screening for lung cancer in Japan. The policy has evolved from the radiographic screening for tuberculosis that has been done since 1951. Beginning in 1987, chest X-rays for lung cancer are offered to persons over 40 years old, and sputum cytology is offered to heavy smokers over 50 years old. In 1986, 460,000 persons over 40 years old were screened by chest X-ray. There were 173 cases of lung cancer found; the detected prevalence was 41.5 per 100,000. Sixty-five % of the cancers were classified as stage 1. Thirty thousand persons were screened by both X-ray and cytology. There were 39 cases found; the detected prevalence was 11.8 per 1,000.

Tominaga presented information on screening for breast cancer in Japan. In 1983, 672,000 women were screened. The primary method of examination was breast palpation and inspection, with follow-up echography or mammography. The number of cases detected was 466; the detected prevalence was 0.69 per 1,000. The Japanese government began to subsidize screening activities in 1987, and the government is also sponsoring evaluation of the efficiency and efficacy of the screening. A randomized trial is not likely to be done. Several nonexperimental methods will be used. These include a case-control study, comparisons of breast cancer incidence and mortality between participants and nonparticipants in screening, and comparisons of breast cancer mortality between areas of high and low rates of screening.

Other Data

J. A. H. Lee (University of Washington, Seattle, WA) reported on trends of melanoma. Most of the available data pertain to melanoma of the skin. In western populations, incidence and mortality from this disease are rising. Among Japanese, the incidence of melanoma of the skin is lower than it is in Europe and North America, but mortality from the disease is also increasing in Japan. In both Japanese and western populations the rate of melanoma for young adults is higher in women than in men.

In his closing comments on this half of the meeting, Morrison summarized recurrent themes of discussion: cancer screening can be valuable and it is the best control measure available for certain cancers. However, screening has risks as well as benefits. People who have false positive tests do not benefit from a screening program. On the contrary, these people suffer as a result of being screened. Typically, false positive screenees outnumber true positives. Programs were described in which the ratios of false positives to true positives were 50–100:1. Therefore, there may be substantial medical risks (in relation to benefit) created by ineffective screening, and the risks may be relatively high even in an effective screening program if the disease is very rare. Persons responsible for setting screening policy (for deciding whether, or when, screening programs should be introduced) should consider whether a particular type of screening has been adequately evaluated and what the avail-

able data or efficacy and predictive value show. Makers of policy should be willing to recommend against screening when the available data best support such a decision, as well as recommending in favor of screening when that is appropriate.

Primary Prevention of Cancer

The second half of the meeting was devoted to the primary prevention of cancer. T. Sugimura (National Cancer Center, Tokyo, Japan) opened the session with a lecture on principles of prevention, and he described relations between basic sciences and epidemiology. He emphasized the role of tumor promoters, some of them ill defined at present. Sugimura concluded with 12 recommendations for cancer prevention. These emphasized moderation in living habits. The recommendations resembled advice for a balanced and happy life given by the ancient Greek philosophers.

The next group of presentations dealt with risk factors in relation to cancer mortality. R. Ross (University of Southern California, Los Angeles, CA) focused on nondietary risk factors. The smoking of cigarettes is most important of these in terms of its preventability and its overall effect on risk of death from cancer. Ross then discussed the recent idea that exercise may affect the risk of colorectal cancer. Next, he reviewed exogenous hormones as causes of cancers at different anatomical sites, indicating the importance of evaluating the overall effects of risk factors; exogenous hormones are likely to be protective for cancer of some sites (and corresponding causes of death), whereas hormones are associated with an increase in risk of death for cancer of other sites.

The presentations of H. Shimizu (Tohoku University, Sendai, Japan) and S. Hino (Nagasaki University, Nagasaki, Japan) were related to a theme raised by Sugimura, that of links between the laboratory and the field. Hino described a Japanese trial designed to break the endemic cycle of human T-cell lymphotrophic virus 1, the first human virus mainly transmitted by a milk-borne pathway. Shimizu showed that migration at a relatively late age to another environment affected the risk of colorectal cancer. This observation may give clues to the carcinogenic process and to the relevant changes in the environment, such as those involving diet.

The current importance of diet in etiological research on cancer was emphasized by the presentation of numerous papers on the topic. Y. Ohno (Nagoya City University, Nagoya, Japan) reported the results of a study on dietary risk factors for prostatic cancer. T. Hirohata (Kyushu University, Fukuoka, Japan) related the risk of breast cancer to diet and other factors. In this study, dietary variables showed only weak associations with risk. R. Sasaki (Nagoya University, Nagoya, Japan) compared the serum carotene levels between Japan and China. S. Lu (Chinese Academy of Medical Sciences, Beijing, China)

described a preventive trial for esophageal cancer with a nutritional intervention including Chinese herbs, vitamins, and trace elements in Lie-Xian County, China. Another preventive trial with nutritional aspects was described by C. H. Hennekens (Harvard Medical School, Boston, MA). This large, well-designed, and well-executed trial evaluates long-term use of β-carotene in decreasing the risk of cancer. Hennekens also described the practical problems and scientific background of such studies. A paper by C. W. Boone (National Cancer Institute, Bethesda, MD) addressed the effects of chemopreventive agents on the risk of cancer in animals and in clinical trials in humans, thus representing another link between the laboratory sciences and epidemiology.

In his overview, Tominaga estimated the reduction in cancer incidence that might be brought about by feasible primary preventive programs. He concluded that an overall reduction of 10% is achievable through control of cigarette smoking; that another 10% reduction is achievable through changes in dietary habits, mainly by lowering the consumption of salt and rice; and that a total of about 27% of cancers might be preventable in Japan. The WHO Geneva headquarters, as well as Doll and Peto, estimated that about 1 of 3 cancers is preventable. This reduction is achievable mainly through control of smoking. These estimates differ from that for Japan, in that only about 10% of cancers in Japan seem to be preventable by control of smoking and that dietary changes may provide prevention of another 10% of cancers. Two major conclusions can be drawn from these figures: (a) experience from other countries is not necessarily directly applicable to Japan; (b) each country should make its own cancer control policy, because conditions differ from country to country. There is a general belief that a high risk of cancer is unavoidable. This is not true; cancer is preventable. The estimate that 1 of 3 cancers is preventable is substantial, especially when compared to the effects of other means of cancer control.

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