Ethical Issues in Cancer Epidemiology and Disease Susceptibility Genes

<viewpoint>

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ABSTRACT

Cancer epidemiology is the branch of epidemiology concerned with cancer. Epidemiology has established scientific evidence about exposure effects within human populations. Molecular epidemiology aims to elucidate the effects of the genetic variation in human cancer etiology. With exposure to an environmental risk factor, carriers of a genetic risk factor show a greater risk of developing sporadic cancer than those without the genetic risk factor due to the gene-environment interaction. In this paper, we discuss the ethical issues in cancer epidemiology using disease susceptibility genes. Since genetic information does not change and is shared with siblings and parents, both informed consent and confidentiality are very important.

Key words : Cancer epidemiology, Genetic information, Ethics, Confidentiality, Informed consent

1. Introduction

Epidemiology is the science of occurrence of diseases in human populations[1]. Disease occurrence is measured and related to different characteristics of individuals or their environment. In other words, epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems[2]. Modern methods of epidemiological inquiry were first developed in the course of investigating outbreaks of infectious diseases in the nineteenth century[3]. However, similar methods are now used in the investigation of the cause and natural history of every type of disease, including cancer. Interest in cancer has grown during the past century as infectious diseases have increasingly been controlled as the result of improved sanitation, vaccination and antibiotics[4]. Cancer epidemiology is the branch of epidemiology concerned with the disease cancer. Epidemiology has established scientific evidence about exposure effects within human populations (e.g., cigarette smoking and lung cancer).

In epidemiological studies, we study the effect of exposure on the outcome. Cancer epidemiologists have studied to answer the question: 'Does the exposure of interest increase the risk of cancer?' Sources of exposure data include questionnaires, diaries, and records[4].

Recent advances in molecular biology have

been applied to epidemiology. Interest in the epidemiological application of measurements of exposure in the human body has recently been growing, with the development of laboratory techniques for measuring active metabolites of carcinogens and the products of their interaction with DNA or proteins (adducts)[4].

Molecular epidemiology aims to determine the effects of genetic variations (e.g., genetic polymorphisms) including gene-environment interactions in human cancer etiology. Although a large part of epidemiological research carries little or no direct risk to the participants of the research, genetic information with personal identifiers (e.g., name, social security number, address, telephone number), which are used in molecular epidemiological research, may lead to discrimination.

In this paper, we discuss the ethical issues in epidemiology and disease susceptibility genes.

2. Study Design of Cancer Epidemiology

Cohort study

Epidemiologists use two basic approaches to compare incidence rates between exposed and unexposed groups[1]. As shown in Fig 1, the cohort study is an observational study in which the starting point is the selection of a study population that has no manifestation of the disease of the interest. Information is obtained to determine which members of this study population are exposed to the factor of interest. The entire population is followed up over time and the incidence of the disease in the exposed group is compared with the incidence of the unexposed group. The cohort study provides the best information about the causation of disease and the most direct measurement of the risk of developing disease. However, the cohort study requires long periods of follow-up, and is not suitable for investigating rare diseases.

In our previous cohort study[5], 2,998 hepatitis B surface antigen (HBsAg) negative subjects and 54 positive subjects in town K were followed from June 1992 to March 1997. Seventy-nine subjects were lost during the study period because they moved from the town. On the basis of 13,735.0 person-years, 20 subjects were newly diagnosed with hepatocellular carcinoma (HCC) among HBsAg-negative subjects while 2 subjects were among positive subjects on the basis of 248.9 person-years. Thus, our previous study revealed that the risk of developing HCC was significantly higher for subjects who were positive for HBsAg (hazard ratio=5.52, 95% confidence interval: 1.29, 23.63, $p<0.05$). Even after controlling for gender and age, positivity for HBsAg was significantly associated with HCC risk (hazard ratio=7.28, 95% confidence interval: 1.62, 32.61, $p<0.01$).

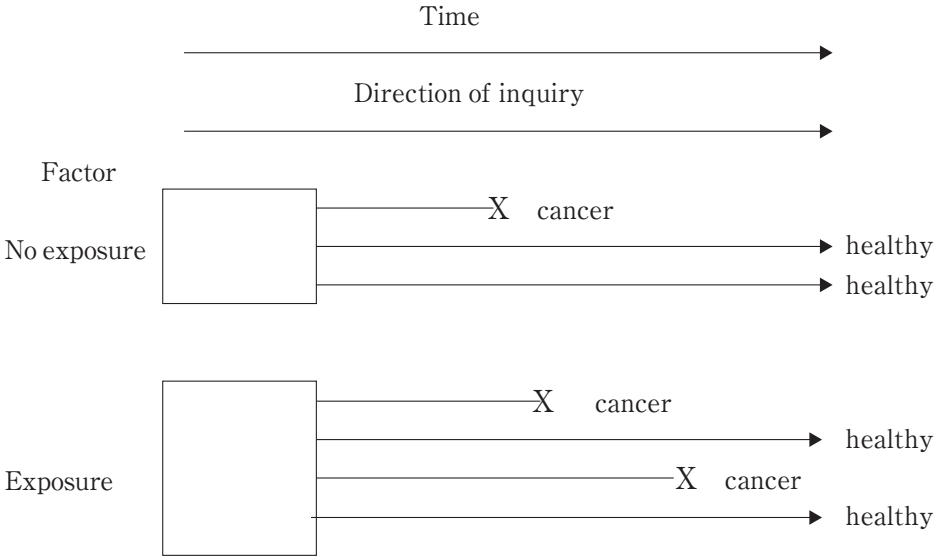


Fig. 1 Outline of cohort study

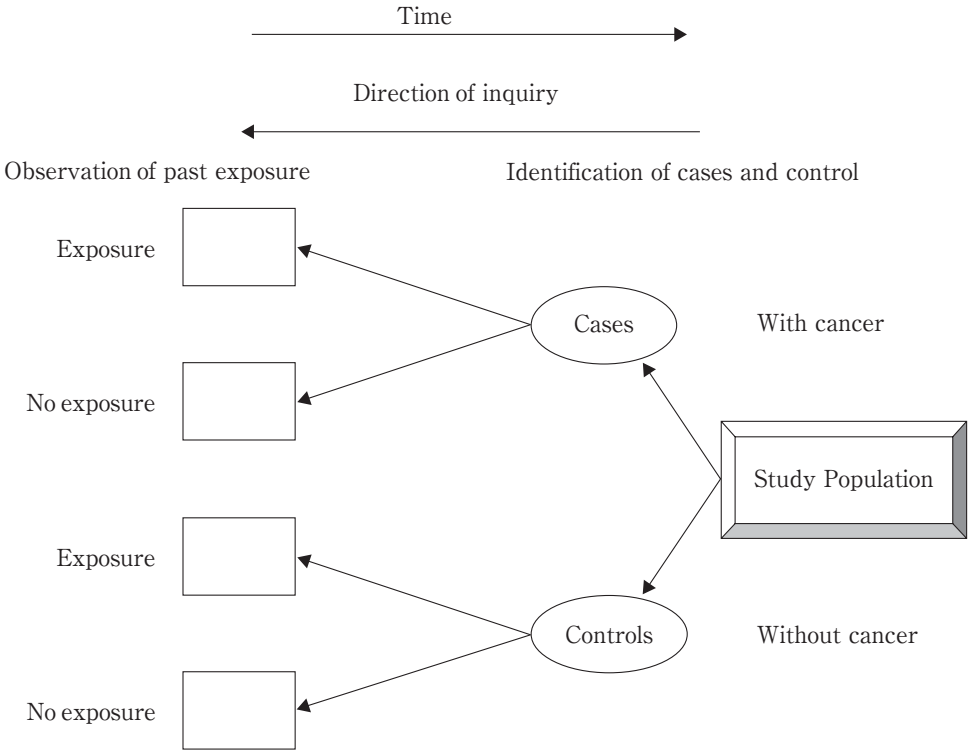


Fig. 2 Outline of case-control study

Case-control study

The case control study is relatively simple and economical to carry out[1]. The case-control study is suitable for investigating the cause of a rare disease but not for rare causes. As shown in Fig. 2, the case-control study is an observational study in which the starting point is the identification of cases and controls. Cases are identified because they are known to have the disease of interest while controls are identified because they do not have the investigated disease. The frequencies of past exposures are compared between cases and controls. In the case-control study, the exposure status of the cases is usually determined after the development of the disease. Questions about past exposures are usually answered by the study subjects or their relatives. Their answers may be influenced by the disease experiences. Exposure is sometimes determined by biological measurements, which may be affected by the disease. This problem can be avoided in the nested case-control study.

The nested case-control study is a case-control study in which cases and controls are drawn from the population in the cohort study[2]. In the nested case-control study, the exposure data are collected before the development of the disease.

In our previous case-control study[6], 89 cases with ovarian cancer were compared with 323 control subjects without ovarian cancer. Seven cases (7.9%) had a history of diabetes mellitus among the 89 cases while 8 controls (2.5%) did so among 323 controls. Thus, our previous study revealed that a history diabetes mellitus was associated with a significantly increased risk of ovarian cancer (odds ratio=2.94, 95% confidence interval: 1.02, 8.49, $p<0.05$). However, when the heaviest non-pregnant weight was simultaneously included in the model as continuous variable, a history of diabetes mellitus failed to remain as a significantly increased risk factor (odds ratio=2.52, 95% confidence interval: 0.86, 7.40).

Cross-sectional study

The cross-sectional study is a study that examines the relationship between diseases and other variables of interest as they exist in a de-

fined population at one particular time[2]. The frequencies of variables of interest are compared between disease-positive subjects and -negative subjects. The prevalence of disease rather than the incidence is normally recorded.

In our previous study[7], 227 males (19.7%) were positive for hepatitis C virus antibody (anti -HCV) among 1151 males in town K. The 227 anti-HCV positive males were compared with 924 negative males. Thirty-nine positive subjects (17.3%) had a medical history of blood transfusion as did 62 negative subjects (6.8%). Thus, our previous study revealed that a history of blood transfusion was a risk factor for anti-HCV positivity (odds ratio=2.65, 95% confidence interval: 1.72, 4.10, $p<0.001$).

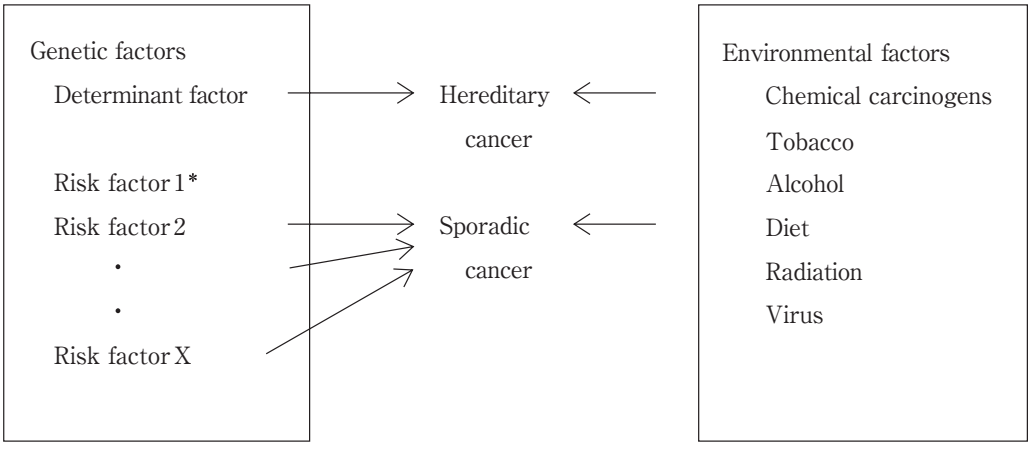
Case-only study

The case-only study is a method that analyzes data from a case series, with assumed or theoretical data on prior distribution of exposure instead of a control group[2]. Epidemiologists use the case-only study design to study the association between environmental exposure and genotype in genetic epidemiology.

3. Genetic Risk Factors and Environmental Risk Factors

Carriers with a determinant genetic factor of a hereditary cancer show a highly increased risk of developing the hereditary cancer (e.g., familial adenomatous polyposis) while carriers with a genetic risk factor of a sporadic cancer have a little risk of developing the sporadic cancer (Fig. 3)[8]. Dozens of genetic risk factors are involved in sporadic cancer. With the exposure to an environmental risk factor, carriers of a genetic risk factor show a greater risk of developing the sporadic cancer than those without the genetic risk factor. In other words, environmental risk factors interact with genetic risk factors (the gene-environment interaction), which put one individual at a greater or smaller risk of sporadic cancer than another. Molecular epidemiological studies have suggested complex interactions between the estrogen receptor and the aromatic hydrocarbon receptor pathways in the gender difference in lung cancer susceptibility. It is possible that circulating estrogen may interact with receptors present in the lung and modulate the expression of polycyclic aromatic hydrocarbon (PAH) metabolizing enzymes[9].

Genetically determined susceptibility to smoking-related cancers may depend on the metabolic balance between phase I and phase II enzymes. Benzo(a)pyrene, one of the most typical PAHs, is ultimately metabolized to the carcinogen BP7,8-diol-9,10-oxide by phase I enzyme CYP1A1. Subsequently, the ultimate carcinogen can be metabolized further to innocuous water soluble metabolites through conjugation with glutathione by phase II enzymes GSTs (Fig. 4). It is likely that individuals with more reactive phase I enzymes and less efficient phase II en-



*Dozens of risk factors are considered to be involved in sporadic cancer.

Fig. 3 Genetic and environmental factors in carcinogenesis

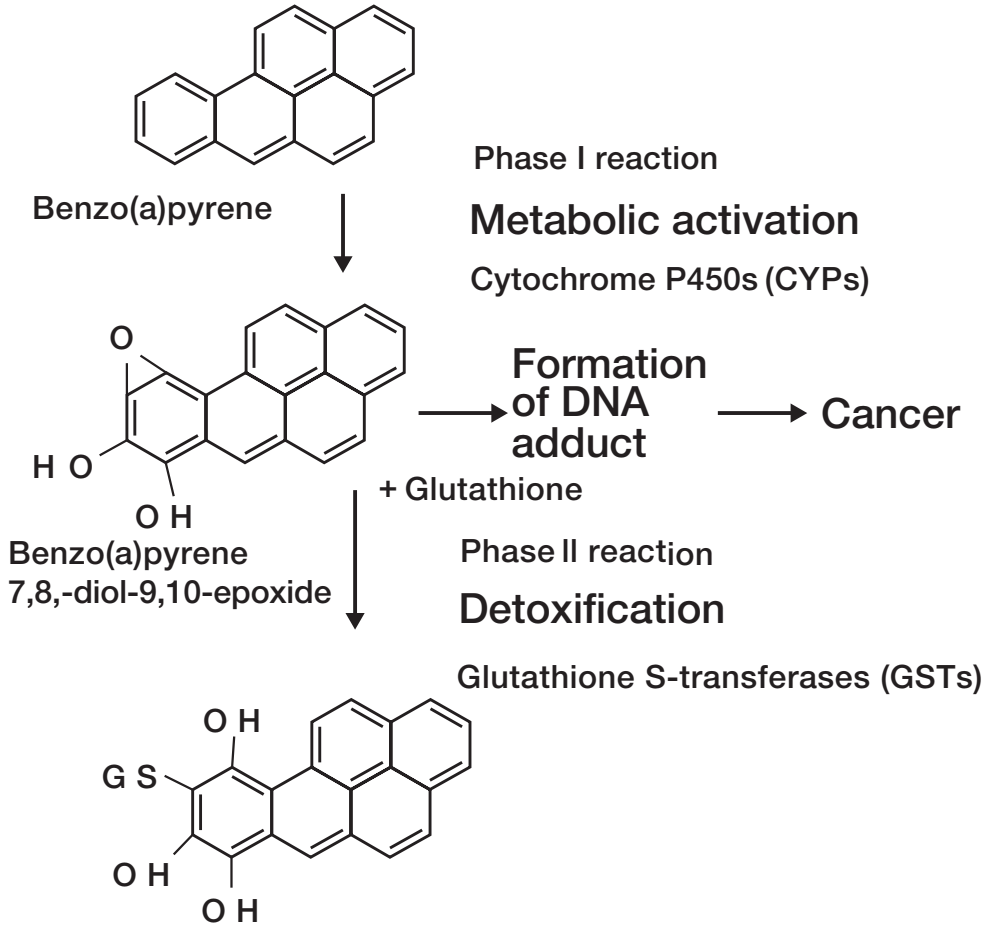


Fig. 4 Metabolism of Benzo(a)pyrene

zymes might be at higher risk of cancer than individuals with the opposite combination. Cigarette smoking is a strong risk factor of lung cancer, but genetically determined variations in the metabolism of tobacco-derived carcinogens may affect individual risk. Smoking-related risk of lung cancer may be more accurately estimated when genetic susceptibility is allowed for as regards both *CYP1A1* and *GST* genotypes. The findings in Japanese population studies to date have revealed high ORs for lung cancer[10]. However, only 10 to 24% of Japanese lung cancer patients display these polymorphism combinations. For non-Asian populations, the relevance of the *CYP1A1 Msp* I and *GSTM1* polymorphisms to lung cancer is questionable, given their low prevalence in both lung cancer and general populations. Combined *CYP1A1* and *GSTM1* genotypes are thus a potential predictor of genetic susceptibility to smoking-related lung cancers in populations where *CYP1A1* alleles are common.

4. Ethical Issues

Ethics in epidemiologic practice

Ethics is the branch of philosophy that deals with distinctions between right and wrong, with the moral consequences of human actions[2]. Ethical principles govern the conduct of epidemiology, as they do all human activities. The ethical issues that arise in epidemiologic practice and research include informed consent, confidentiality, respect for human rights, and scientific integrity.

Genetic information and epidemiology

In molecular epidemiology, epidemiologists use genetic information with personal identifiers (e.g., name, social security number, address, telephone number), which may lead to discrimina-

tion, stigmatization, embarrassment, and ostracism[11].

Since genetic information does not change and is shared with siblings and parents, both informed consent and confidentiality are very important. Thus, suggestions have been made for the regulation of genetic research (definitely, including cancer epidemiology) and DNA databanks[12]. The suggestions include public disclosure of intent to establish the DNA databank, justification for research, prior written authorization and approval that sets forth the uses and purpose of research, guaranteed individual access to the sample and the records, the right to request return or destruction of the sample, the right to correct inaccurate information, strict security measures and protection against unauthorized or third party access, and notification of new information with potential impacts on health.

"Ethical Principles of Research on the Human Genome and Genetic Analysis" in Japan

In Japan, a Sub-committee on Human Genome Research (Bioethics Committee, Council for Science and Technology) was created in December 1999 to examine the approach to be taken in human genome research, and following the discussion therein, proclaimed the "Fundamental Principles of Research on the Human Genome" on June 14th, 2000. Following this, three ministries (the Ministry of Health, Labour and Welfare, the Ministry of Economy, Trade and Industry, and Ministry of Education, Culture, Sports, Science and Technology [MEXT]) announced the "Ethical Principles of Research on the Human Genome and Genetic Analysis" on March 29th, 2001. (http://www2.ncc.go.jp/elsi/index.htm) These principles define the ethical framework that should be respected by those who are engaged in human genome research such as scientists and physicians in Japan.

Informed consent for the participants

Participants have the right to make a voluntary decision either to take part in a study or to refuse. Epidemiologists should not induce or intimidate participants. Epidemiologists should give participants the necessary information, including specific characteristics of genetic information. Epidemiologists should judge each individual participant's level of understanding, and should use easy words so that participants are able to understand what they are told and to make a reasoned choice.

Informed consent for surrogates

When the potential participants are not competent (e.g. those with cognitive impairments and children), epidemiologists may seek consent from surrogates (e.g. a partner, relative, or parent)[13]. When children are 15 years old and older, epidemiologists should seek consent not only from their parents but also from the children themselves. When children do not want to join the study, their opinions should be respected whether they are 15 years and older or not.

Informed consent for the general population

The general population may misunderstand genetic epidemiology unless they know the difference between genetic risk factors and determinant genetic factors. Genetic epidemiology aims to establish the strategy of preventive medicine based on genetic information. Carriers of a genetic risk factor can prevent the development of a sporadic cancer by avoiding exposure to environmental risk factors. Education for the general population is thus recommended.

Institutional review boards (IRBs) Reform in US

Recently, institutional review boards (IRBs) review "too much, too quickly, and with too little expertise," and many IRBs spend "only 1 or 2 minutes of review per study." [14] This inadequate situation of protection of the rights and welfare of human subjects in medical research is now being intensively discussed in the US.

Annas warned that, with risk of genetic research, "racism" could be replaced or supplemented by "genism."[15] As part of the IRB reform process, efforts should focus on taking the

entire consent process seriously. The goal of informed consent is to provide protection by making sure that potential research subjects understand the research they are being asked to volunteer for, its risks, its benefits, and its alternatives.

We should not forget that informed consent is a process, and only after that process occurs it is documented with a consent form. Beskow's paper will be helpful in preparing a consent form for population-based research involving genetics[16] .

Genetic counseling

Genetic counseling should be provided for the participants when epidemiologists intend to inform each participant personal about genetic information[17]. Candidates should consult with a genetic counselor in order to decide whether they will get personal genetic information. After getting their own genetic information, follow-up counseling should be provided.

Notification of cancer (truth telling)

In Japan, not all cancer patients are told that they are suffering from cancers, nor do doctors in Japan always notify their patients about the name of the cancer[18]. Most doctors do so on a case-by-case basis after consultation with the patient's family. When cancer patients do not know the truth, epidemiologists should not tell the truth. In that case, epidemiologists should ask cancer patients to take part in a study not for cancers but for assumed diseases, which they are notified of.

Confidentiality

Epidemiologists should respect participants' right to privacy. Epidemiologists may correct and store their personal data. If such data are disclosed to a third party, they may be harmful to the participants. Genetic information with personal identifiers may lead to discrimination. Epidemiologists should make arrangements for protecting the confidentiality of personal data, for example, by omitting personal identifiers, and limiting access to the data.

Dissemination of findings of public health importance

Epidemiologists should inform scientific peers of their study results by publications in the scientific literature or presentations at scientific conferences[19]. Epidemiologists should disseminate findings of public health importance as well.

6. Conclusion

In this paper, we discuss the ethical issues in cancer epidemiology using disease susceptibility genes. Since genetic information does not change and is shared with siblings and parents, both informed consent and confidentiality are very important. The general population may misunderstand genetic epidemiology unless they know the difference between genetic risk factors and determinant genetic factors. Education for the general population is thus recommended.

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