Heritable Susceptibility Factors for the Development of Cancer

William W. AU*

Genetic susceptibility/Polymorphic genes/Chemical metabolism/DNA repair/Cancer.

High frequencies of inherited DNA sequence variations (polymorphisms) are found in the human population. The involvement of polymorphic genes (especially for chemical metabolism and DNA repair) in the development of cancer is under intensive investigation. In our studies, we have irradiated blood lymphocytes from normal non-smokers with γ-rays or UV-light to investigate genotypes and DNA repair functions. We found that XRCC1 399Gln and XRCC3 241Met were deficient in the repair of γ-ray- but not UV-light-induced DNA damage that led to the expression of chromosome aberrations; therefore the variant genotypes are defective in base excision repair. The reverse was found with XPD 312Asn and XPD 751Gln; therefore they are defective in nucleotide excision repair. XRCCI 194Trp, OGGI 326Cys and APEI 148Glu had no DNA repair deficiency based on our experimental conditions. In another study, we investigated the role of some of these genes on the development of lung cancer. We found a significant increase of chromosome aberrations in patients and controls that had the XPD 751Gln and GSTM1 null genotypes, indicating a mechanistic causation of the disease. Therefore, inheritance of susceptibility genes can have significant impact on disease burden in the population. On the other hand, there are many questions that need to be addressed in order to evaluate the impact of susceptibility on cancer. These questions include the understanding of combinations of different polymorphic genes for susceptibility and of specific disease susceptibility for different ethnic populations.

INTRODUCTION

With the exception of identical twins, the genomic sequence in one individual is uniquely different from another. The variation in genomic sequences can be caused by a variety of mechanisms such as single nucleotide changes, DNA sequence deletions or duplications. Some of the DNA changes are innocuous. Other changes cause us to be phenotypically different from the each other and may cause health consequences. In addition, some changes are inherited in a Mendelian fashion while some are developed in somatic cells. Understanding the cause of these changes and the functional significance of the alterations will help us in developing better disease prevention program.

GENETIC PREDISPOSITION TO CANCER

Inheritance of certain mutated genes can cause an individual to have exceptionally high risk for the development of cancer. An example is mutation in the XP gene among xeroderma pigmentosum patients.1 Without adequate protection from exposure to sunlight, over 90% of these patients develop multiple and recurrent skin tumors, mostly basal- and squamous cell carcinomas by early adulthood. The disease is inherited as an autosomal recessive trait and the prevalence is approximately 1–4 in 10^6 live births (Table 1). Another example is inheritance of mutations in the BRCA1 gene that predispose females to develop breast or ovarian cancer.2 Heterozygotes for the mutated gene have an 80% chance of developing cancer in the life time with the median age of around 50 years. In breast cancer cells, both copies of the gene are mutated, indicating that the mutations involved are recessive and the gene belongs to the category of tumor suppressor genes. The prevalence of the BRCA1 mutant alleles is approximately 1–5 in 10^3 live births.

The two cancer predisposing genes as discussed above are involved with DNA repair activities. The XP gene is responsible for the repair of UV-light induced DNA damage. Different loci representing at least eight complementation groups can cause the XP disease. The BRCA1 gene is involved with the repair of DNA double strand breaks. Besides the BRCA1 gene, mutations in other genes such as BRCA2 contribute to increased risk for breast cancer. The prevalence of the highly penetrant XP and BRCA1 mutated

*Corresponding author: Phone: 409-772-1545, Fax: 409-772-9108, E-mail: william.au@utmb.edu

Department of Preventive Medicine and Community Health The University of Texas Medical Branch 700 Harborside Drive, 2.102 Ewing Hall, Galveston, TX 77555-1110, USA.

J. Radiat. Res., 47: Suppl., B13–B17 (2006); http://jrr.jstage.jst.go.jp
Polymorphisms in the genome. There may be large scale sequence changes such as copy number polymorphisms in the genome. There are several variant genotypes in metabolizing genes that are associated with cancers that are related to exposure to environmental mutagenic chemicals.

A major interest on polymorphisms in chemical metabolism and DNA repair genes is the identification of genetic risk factors for cancer. Early studies in this field were encouraging because several variant genotypes in metabolizing genes were reported to be significantly associated with the development of cancer, such as lung cancer among cigarette smokers. However, these early studies had focused on single genes and small sample sizes and focused on single genes. Consequently, subsequent studies using much larger populations did not substantiate many of the previous observations. Nevertheless, a meta-analysis of published studies indicates that inheritance of the GSTM1 null genotype is most likely involved with the development of lung cancer among cigarette smokers.

The discovery of high prevalence of variant alleles in DNA repair genes was unexpected because repair enzymes from these genes are needed to perform essential and precise functions. Of significant interest is the observation of DNA polymorphisms that are expected to cause altered amino acid composition in the repair enzymes. Therefore, the findings sparked renewed interest in elucidating the relationship between polymorphic genes and cancer. Several reports have indicated that some variant genotypes in DNA repair genes were associated with cancers that are related to exposure to environmental mutagenic chemicals. However, unlike polymorphisms in chemical metabolizing genes, the functional significance of the observed associations may depend upon the knowledge regarding the impact of the polymorphisms on DNA repair activities.

Table 1. Distribution of variant gene alleles in populations

| Genotypes         | Frequency in the population |
|-------------------|----------------------------|
| For high penetrant genes |
| Xeroderma pigmentosum | < 0.001%                   |
| BRCA1 for breast cancer | < 0.1%                    |
| For the low penetrant gene |
| GSTM1 null        | 50%                        |
| XPD 751Gln        | 18%                        |
| NAT2* in different populations |
| African           | 71%                        |
| American Indian   | 50%                        |
| Central/West Asian| 74%                        |
| Chinese/Japanese  | 37%                        |
| European          | 75%                        |
| Eskimo            | 23%                        |
| South Pacific Islander | 35%                      |

* a variant genotype.

GENETIC RISK FACTORS FOR CANCER

Genes is rare in the population. However, it is believed that common variant alleles of these and other DNA repair genes are also involved with risk for cancer.

POLYMORPHISMS IN CHEMICAL METABOLISM AND DNA REPAIR GENES

Recent genomic studies have documented surprising plasticity in the human genome. The plasticity is mainly due to DNA sequence variations from one individual to another that is based on single nucleotide changes, known as single nucleotide polymorphisms (SNP). From various estimates, the frequency of SNPs may be around 1 in 1000 nucleotides. There can be as many as 7 million common SNPs with an allelic frequency of more than 5% across the entire population. The frequency of these variant alleles can be substantially higher than mutations in genes that cause cancer (Table 1). On the other hand, there can be numerous very rare alleles that are present in only a single individual. In addition, there may be large scale sequence changes such as copy number polymorphisms in the genome. An important question to address is what role these variations play in our lives, especially on genes that are essential to our daily functional activities and our health. A recent focus is on SNP polymorphisms of chemical metabolizing and DNA repair genes.

A major interest on polymorphisms in chemical metabolizing genes is their metabolism of environmental toxic chemicals and the effect on the development of cancer. Early studies in this field were encouraging because several variant genotypes in metabolizing genes were reported to be significantly associated with the development of cancer, such as lung cancer among cigarette smokers. However, these early studies had frequently used small sample sizes and focused on single genes. Consequently, subsequent studies using much larger populations did not substantiate many of the previous observations. Nevertheless, a meta-analysis of published studies indicates that inheritance of the GSTM1 null genotype is most likely involved with the development of lung cancer among the cigarette smokers.

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FUNCTIONAL CHARACTERIZATION OF DNA REPAIR GENES

Studies have been conducted to investigate the role of polymorphisms in DNA repair functions. An approach is to use biomarkers to elucidate the biological activities and to relate such activities with the presence of the variant genotypes. Using the challenge assay, we studied the role of polymorphisms in certain base-excision and nucleotide-excision repair genes on the repair of γ-ray- and UV-light induced chromosome aberrations. The use of chromosome aberrations as the biomarker has the distinct advantage of identifying specific aberrations that are due to incomplete repair of DNA damage from each inducing agent. In this case, chromosome- and chromatid-type aberrations were documented after exposure to γ-ray and UV-light, respectively. Our data show that XRCC1 399Gln and XRCC3 241Met were deficient in the repair of γ-ray- but not UV-light-induced chromosome aberrations; therefore the variant genotypes are defective in base excision repair. XPD 312Asn and XPD 751Gln are deficient in the repair of UV-light- but not γ-ray-induced chromosome aberrations; therefore they are defective in nucleotide excision repair. On the other hand, XRCC1 194Trp, OGG1 326Cys and APE1 148Glu probably have limited alterations in repair activities compared to the wild-type genotypes based on our experi-

J. Radiat. Res., Vol. 47, Suppl. B (2006); http://jrr.jstage.jst.go.jp
mental conditions. By using chromosome aberrations as the biomarker, the experimental protocol is useful for distinguishing deficiency in the two major DNA repair pathways, i.e. base- and nucleotide-excision repair pathways. In addition, using physical instead of chemical agents as DNA damage inducers, the potential complications from inherited variations in chemical metabolizing genes can be avoided. These observations have been confirmed in a separate investigation using a large population. The latter study was based on the observation of baseline chromosome aberrations rather than on the response to challenge. Other investigators have used a variety of other biomarkers for similar studies, such as DNA adducts and sister chromatid exchanges. These publications have been reviewed recently.

POLYMORPHIC GENES AND LUNG CANCER

Since the development of cancer involves the induction of multiple mutations and the progression through different stages, recent investigations are focused on the interactions of multiple susceptibility genes and the use of biomarkers. Harms et al., reported that the functionally deficient XPD 751Gln genotypes were significantly associated with increased chromosome aberrations for the development of lung cancer. The susceptibility genotypes interacted with the null GSTM1 metabolizing genotype to significantly enhance the risk. Increased chromosome aberrations was also observed with other functionally deficient variant genotypes XRCC1 399Gln and XRCC3 241Met. However, the differences were not significant. Since the expression of chromosome aberrations in these smokers were caused by exposure to chemicals, one would expect that deficiency in the nucleotide excision repair pathway might be more involved with this process (XPD 751Gln) than that from base-excision repair genes (XRCC1 399Gln and XRCC3 241Met). The described rationale was supported by an epidemiological investigation by Sorensen et al., who reported associations between susceptibility haplotype [ERCC1, Asn118Asn(A), ASE-1 G-21A(G), RAI IVS1 A4364G(A)] and cigarette smoking for the development of lung cancer. On the other hand, Kiuru et al., found that the XRCC1 280His but not the XRCC1 399Gln genotypes was significantly involved with the expression of chromosome aberrations among lung cancer patients.

INvolvement in Multistage Carcinogenesis

It is well-known that the development of cancer is a multistage and prolonged process. Initiation of the process is primarily based on the interactions between susceptibility (both genetics and acquired) and exposure to carcinogenic environmental agents. Their continued interactions are probably needed to “fix” the initiated cells towards the pathway to become neoplastic cells. Along the pathway, multiple cellular changes are required and some of these changes have been documented using sophisticated laboratory techniques, e.g. alteration in cell cycle control mechanisms and avoidance of the programmed cell death phenomenon (apoptosis). With this very simple description of the carcinogenic process, one can understand that alteration in the expression of multiple genes is needed for the carcinogenic process to complete its course. Altered gene expression can be accomplished by somatic mutation events from exposure to the carcinogenic agents or by inheritance of susceptibility genes. Table 2 shows a list of some genes that are involved with the carcinogenic process. Genes that belong to the chemical metabolism and DNA repair categories have been described earlier. Most of the genes in these two categories have inherited variant genotypes that can affect their functions. Additional genes that contribute to the carcinogenic process belong to the DNA modification and cell proliferation control categories. Inherited variant genotypes have also been identified in genes in these two categories. Therefore, having inherited various combinations of these genes will most certainly increase the risk of developing cancer for individuals who are also exposed to carcinogenic agents. On the other hand, one may also consider the possibility that most cancers are caused by exposure to carcinogenic agents and inheritance of several susceptibility genes. Identification of the agents and genes is critically important in the cancer prevention program.

OTHER CONSIDERATIONS FOR POLYMORPHIC GENES

Currently, the major attention has been focused on the interactions between polymorphic genes and environmental

| Gene categories               | Genes    | Relevance to cancer                        |
|-------------------------------|----------|--------------------------------------------|
| Chemical metabolism           | CYP1A1, GSTM1 | Activation and detoxification of xenobiotics in vivo, and facilitation of their elimination. |
| DNA repair                    | XRCC, XPD | Repair of induced DNA strand breaks, small lesions, adducts and other DNA damage |
| DNA modification              | MTHFR    | Methylation of DNA that causes normal or abnormal gene expression |
| Cell proliferation control    | p53, BRCA | Involvement with cell cycle control and apoptosis |

Table 2. Inherited susceptibility genes for the development of environmental cancer
toxic substances to increase risk for cancer. However, it is clear that these variant versions of polymorphic genes can influence the development of other health effects also. A critical area of concern is their effects on transplacental induction of birth defects. Another is the effect on the induction of germ cell damage that can be transmissible to future generations.

Quantitative population genetic studies provide information regarding the prevalence and contribution of inherited mutations in the development of cancer.26 These studies indicate that highly penetrant and dominant mutations that cause childhood cancer or that interfere with reproduction are rapidly removed from the population. The fact that these mutations are maintained at low frequencies in the population indicates that new mutations are induced in every generation. On the other hand, mutations that have low penetrance and cause late-onset cancers are maintained at a higher frequency. Polymorphisms in genes that are associated with cancer can be maintained at very high frequency (e.g., a frequency of up to 50% for GSTM1 null that is associated with lung cancer). These polymorphisms are maintained in the population for generations, i.e., can be much older in human history than the highly penetrant and dominant mutations. The polymorphic genes can have significantly different frequencies in different populations (Table 1), indicating that there are some selection pressure for their maintenance. However, very little is known about the origin of these polymorphisms. Nevertheless, they are induced by mutational mechanisms, served some useful functions in the past, maintained by some selection pressure, passed on from generations to generations and may affect individual responses to environmental toxic substances. Such knowledge may be helpful in understanding why certain populations may have higher predisposition to specific cancer than others.

CONCLUSION

Inheritance of certain mutated genes can cause cancer and other serious health problems in humans. Although these highly penetrant genes are rarely found in the population, more common variant alleles of these genes have been expected to influence our risk for disease. Recent findings have shown that polymorphisms in chemical metabolizing and DNA repair genes are associated with the development of cancer. Since these variant genes are common, they may have large impact on disease burden in the population. More work needs to be focused on understanding the function, induction and maintenance of these variant genotypes in the population. Such knowledge can help us in improving health and fitness in humans.

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Received on April 22, 2005
1st Revision received on June 21, 2005
Accepted on July 8, 2005

J. Radiat. Res., Vol. 47, Suppl. B (2006); http://jrr.jstage.jst.go.jp