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Cancer Risk Related to Genetic Polymorphisms in Carcinogen Metabolism and DNA Repair

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Abstract. Chemical carcinogenesis involves metabolism in the body of the carcinogen to the ultimate carcinogen and its interaction with DNA. There is considerable interindividual variation in the metabolic ability to activate as well as detoxify the carcinogens and in the ability to repair the carcinogen-DNA adducts. In many cases such differences occur as genetic polymorphisms and form the basis for variation in susceptibility to carcinogens and thereby to cancer risk.

The activation mechanism is particularly related to the cytochromes P-450 (CYPs), and four of these are known to activate carcinogens: CYP1A1, CYP1A2, CYP2E1, and CYP3A4. Increased cancer risk has been related to polymorphisms in the CYPs and other activating enzymes.

The DNA repair mechanisms show considerable complexity, and deficient repair mechanisms in certain human disorders are clearly related to increased cancer risk. Yet, there is no unambiguous epidemiological evidence available for cancer risk among individuals in general. In vivo methods have to be refined and developed for use in epidemiological studies.

The initial events in chemical carcinogenesis are often metabolism of the carcinogen to reactive intermediates and an interaction of these with DNA. Large inter-individual variation in these initial processes has been demonstrated and related to the large variation in susceptibility to chemical carcinogens. Moreover, the variation has been related to genetic polymorphisms. In this review we give an update of the current knowledge in this area.

Ever since the original work by the Millers (Miller & Miller, 1982), it has been known that metabolic activation is a prerequisite for the toxicity of many foreign compounds, particularly with respect to mutagenesis and carcinogenesis (Guengerich & Lieber, 1985; Gonzalez et al.,1987; Shimada et al.,1989). The increasing awareness of genetic regulation, particularly appearing as polymorphism, of the enzymes involved in xenobiotic metabolism naturally has generated hypotheses regarding associations to cancer risk.

In the context of metabolism of chemicals, "polymorphism" means the presence within a population of at least two groups with distinctly different ability of metabolizing xenobiotics. At the DNA level this appears extremely common (Jeffreys, 1979). Presently, a polymorphism is defined by a frequency in the population of at least 1% of at least two phenotypes (Vogel & Motulsky, 1982). Polymorphisms are recognized at all steps of xenobiotic metabolism, including e.g. three or more cytochrome P450 species, N-acetyltransferase, sulfoxidation or a related reaction, glutathione S-transferase, probably S-methylation, sulfotransferases and glucuronyl transferases, as well as other steps in the carcinogenic process, e.g. DNA repair processes.

The purpose of the present review is to discuss the present evidence of associations between genetically founded heterogeneity with respect to DNA repair mechanisms and with respect to foreign compound metabolism, mainly in terms of polymorphisms, and the risk of cancer.

Carcinogen Activation/Inactivation Polymorphisms and Cancer Risk.

Cytochrome P4502D6 ($P450_{DB}$) polymorphism.
This cytochrome P450 is controlled by an autosomal recessive gene resulting in its absence in homozygous recessive individuals (dd), who comprises approximately 7% of Caucasians (Eichelbaum et al.,1979; Mahgoub et al.,1977). The dd genotype termed poor metabolizers (PM) have minimal or no capacity for metabolism of specific substrates opposed to extensive metabolizers (EM). The measurement of metabolic capacity is used for phenotyping or genotyping, the latter by dividing the EM's into heterozygous (dD) and homozygous (DD) according to the rate of metabolism. The methods usually involve oral administration of e.g. debrisoquine, sparteine, dextromethorpan, metoprolol, or codeine and determination of ratios of mother compound and metabolite in urine collected for 8-12 hr. The molecular biology of the enzyme has been studied in detail, including DNA sequencing and identification of some of the alterations responsible for its absence (Meyer, 1990). By means of PCR and RFLP of leucocyte DNA

more than 90% of subjects may be genotyped and the specific gene alterations determined (Tyndale et al.,1991).

A number of epidemiologic studies have presented evidence for an association between the CYP2D6 polymorphism and the risk of cancer (Caporaso et al.,1991). In the initial study of this possibility Idle *et al.* (Idle, 1981) found an increased proportion of EM of debrisoquine among native Nigerians with various gastrointestinal tumours and potential aflatoxin exposure compared to healthy controls. Similarly, in a study of 124 Caucasians with gastric cancer and 155 controls with non-malignant disease the EM phenotype was overrepresented among the cases (Roots et al.,1986), with an odds ratio of 3.2 (95% CI: 1.1-8.9, (Loft, 1990).

In a study of 245 patients with lung cancer and 234 controls (Ayesh et al.,1987) with chronic obstructive lung disease, 'EM' was more frequent among the cases, the odds ratio being 6.1 (95% CI: 2.0-18.5). Reassessment of the original data (Caporaso et al.,1989) with more correct cut off points for the metabolic genotyping and attempted control of potential confounding gave even more striking results. Thus, male smokers who were homozygous EM and had been exposed to asbestos (odds ratio 18.4) or PAH were at highly increased risk of the smoking associated squamous (odds ratio 7.9) and small cell (odds ratio 12.7) cancers compared to heterozygous EMs and PM's. In another study of 96 lung cancer cases and 92 controls with careful control of confounders the black and Caucasian EM's were at 6-fold and 11-fold increased risk (Caporaso et al.,1990). Other studies, probably not so well controlled, have supplied less convincing results. In a study of 270 lung cancer patients and 270 controls (Roots et al.,1988) no significant difference was found, the odds ratio of EM being 1.7 (95% CI: 0.9-3.0) (Loft, 1990). In a subset with age below 50 years EM's were overrepresented among the cases. Law *et al.* (Law et al.,1989) reported significantly fewer of the PM phenotype, i.e. two among 104 lung cancer patients than among 104 controls (9 PM) matched for age, sex and smoking history but possibly not for medication. Speirs *et al.* (Speirs et al.,1990) reported a PM frequency of 8 persons among 82 lung cancer patients compared to historical frequencies of 7%. In a French study there were 10 PM's among 153 lung cancer cases compared to 20 among 254 controls, which was not of statistically significant at the 5% level (Duche et al.,1991).

Evidence of associations between the CYP2D6 polymorphism and the risk of other forms of malignant disease is weaker or negative. With respect to bladder cancer one study (Cartwright et al.,1984) of 122 cases and 94 controls showed no difference, whereas a study of 95 cases and 110 controls showed an excess of EM's among patients with aggressive bladder cancer (Kaisary et al.,1987), although this association appeared in post hoc analysis. In a third study (Cartwright et al.,1984) regarding bladder cancer a tendency was seen for lower metabolic ratios, an attribute of the EM phenotype, in 125 bladder cancer cases compared to 556 healthy and younger control subjects. A study on 110 patients with malignant lymphoma and 337 controls (Philip et al.,1987a) showed no significant association with the CYP2D6 polymorphism.

The conclusion regarding the CYP2A6 polymorphism and cancer risk appears to be that such an association is well supported by epidemiological evidence with respect to lung cancer and, so far, less well documented for gastric cancer. Three major problems are however, yet to be solved. Firstly, no potential carcinogen is activated by CYP2D6 in vitro. Secondly, this enzyme is mainly expressed in the liver and is thus difficult to associate with lung cancer involving inhaled substances. Thirdly, no relevant animal model is available for confirmation of any association. At present particularly the first two arguments render a causal relationship between the EM phenotype and cancer difficult to establish. Another and perhaps more likely possibility is that the CYP2D6 polymorphism is linked to another determinant of cancer risk, e.g. an oncogene or tumour suppressor gene.

AH locus polymorphism.

The AH locus encodes a cytosolic Ah receptor which is involved in the regulation of an enzyme battery, consisting of CYP1A1, CYP1A2 and four phase II reaction (see Nebert, 1989 for a review). A number of carcinogenic compounds including polyaromatic hydrocarbons such as benzo[a]pyrene, plant flavones such as ß-naphthoflavone, and TCDD induce these enzymes through interaction with the Ah receptor. CYP1A1 and CYP1A2 are responsible for the metabolic activation of polyaromatic hydrocarbons and aromatic amines to proximate carcinogens, respectively. The expression of the Ah receptor mediated inducibility behaves as an autosomal recessive trait between two strains of inbred mice. By using aryl hydrocarbon hydroxylase (AHH) as a marker of CYP1A1 inducibility, Nebert demonstrated in a series of studies the importance of the Ah (the term in mice) locus polymorphism and route of administration for the risk of cancer induced by polyaromatic hydrocarbons, in casu benzo[a]pyrene (Nebert, 1989). Thus, AHH inducible mice have a high cancer risk from topically administered benzo[a]pyrene, which is locally bioactivated, but a low risk from orally administered carcinogen, which is removed by first pass metabolism by the induced enzymes in the liver, where detoxification such as glutathione conjugation is abundant. By contrast, non inducible mice have a low risk from topically administered carcinogens, but a high

risk of systemic cancers after oral administration, lacking the first pass metabolism capacity.

In humans, several attempts have been made to study the regulation of the AH receptor enzyme battery, particularly in relation to the risk of lung cancer after smoking, i.e. topical exposure to polyaromatic hydrocarbons and other carcinogens. The inducibility of AHH activity was originally reported to be trimodally distributed in cultured mitogen activated lymphocytes, suggesting genetic regulation, which was later supported by family and twin studies (Kellermann et al.,1973; Atlas et al.,1976). In three out of four studies patients with lung cancer have been shown to have, on average, a higher AHH inducibility in cultured lymphocytes than control subjects (Kellermann et al.,1973; Gamberg et al.,1979; Kouri et al.,1982; Paigen et al.,1977). CYP1A1 and AHH activity are expressed in lung tissue, particularly in peripheral airways and bronchiolar and alveolar epithelium from smokers (McLemore et al.,1990; Anttila et al.,1991). Moreover, peripheral lung cancers appeared to be related to a high CYP1A1 expression ((Anttila et al.,1991).

A restriction length polymorphism (RFLP) involving the restriction enzyme *Msp I* of the CYP1A1 gene has been described (Bale et al.,1987). High inducibility cosegregated with a 1.9 kb allele in a family study of 15 Eastern Mediterranean individuals (Petersen et al.,1991). In a study on 172 japanese an association was shown between this polymorphism and lung cancer (Kawajiri et al.,1990). The frequency of the 1.9 kb allele was significantly increased in 23 patients with squamous cell cancer. However, in a similar, but much larger study of 221 Norwegian lung cancer patients and 221 controls no difference was found with respect to the *Msp I* polymorphism (Tefre et al.,1991). One possible explanation for the apparent discrepancy may be differences in allele frequency, i.e. 0.31 as opposed to 0.115 for the 1.9 kb allele in the Japanese and Norwegian populations, respectively (Tefre et al.,1991).

The expression of CYP1A2 in the liver is also under the AH receptor control and is substantially increased by smoking (Sesardic et al.,1988). Thus the AH inducibility has been estimated by studying the hepatic drug metabolism of the probe drug antipyrine (Kellermann et al.,1980), which is supposed to be a substrate of CYP1A2 as well as other CYP forms (Loft & Poulsen, 1989; Loft, 1990). In 57 lung cancer patients the half-life of antipyrine was decreased compared to 57 controls matched for smoking (Kellermann et al.,1980). Using the average half-life as discriminator the odds ratio can be calculated to 4.3 (95% CI: 2.0 to 9.4). Similarly, increased clearance or metabolite production rate or decreased half-life of antipyrine has been found in patients with cancer of the liver (odds ratio 6.9), pancreas (odds ratio: 90), testis (odds ratio: 4.4) and breast (odds ratio 3.5) as well as malignant lymphoma (odds ratio 4.4) compared with appropriate controls, as summarized in (Loft, 1990). The major problem with this approach is the lack of knowledge regarding the effect of the cancer disease *per se* on the metabolism of antipyrine and similar compounds, which is substantially influenced by environmental factors and physiologic as well as pathologic conditions (Poulsen & Loft, in press). Ideally, the association between CYP1A1 and 1A2 expression and cancer risk should be studied prospectively. Indeed, the capacity of CYP1A2 in the liver may be estimated by means of metabolite ratios from dietary ingested caffeine in spot urine samples (Campbell et al.,1987; Kalow & Tang, 1991; Vistisen et al.,1992). Thus, large scale prospective studies and nested case control designs, involving urine samples from biological banks, are technically and practically feasible.

The conclusion regarding the AH locus polymorphism and cancer risk is that the association is mechanistically well founded, but that conclusive epidemiological evidence awaits a more detailed characterization of the genotypes and data from prospective studies.

Acetylation polymorphism.

The first recognized polymorphism of foreign compound metabolism concerned N-acetylation reactions. The report dates back to 1954 (Vogel & Motulsky, 1982). The capacity for N-acetylation of amines is under autosomal recessive genetic control dividing the population into slow and fast acetylators with approximately equal frequency in Caucasians (Clark, 1985). The fast acetylators may be further characterized as heterozygotes and homozygotes according to their acetylation capacity. The capacity of O-acetylation is under the same genetic control as N-acetylation and both reactions are important in metabolic activation and deactivation of environmental carcinogens, such as arylamines (Hein, 1988). A number of amine drugs, including isoniazid, dapsone and sulfadimidine, have been used for determination of the acetylator phenotype, usually involving oral administration and measurement of metabolic or recovery ratios in plasma, saliva or urine. A simpler approach takes advantage of the fact that a metabolite of caffeine is acetylated and the phenotyping by means of urinary metabolites of dietary caffeine has proven just a accurate as standard methods involving sulfadimidine (Grant et al.,1983; Grant et al.,1984). Lately, the molecular biology of the acetylation polymorphism, including the genetic alterations, has been described (Blum et al.,1991). Thus, PCR and RFLP assays are becoming available for genotype determination from e.g. leucocyte DNA.

The notion that the N-acetylation polymorphism may be associated with cancer risk was founded by the observation that the acetylation of the carcinogenic arylamines, benzidine (Glowinski et al.,1978) and 2-aminofluorene (Flammang et al.,1987), by human liver preparations was consistent with polymodality. The arylamines are recognized as bladder carcinogens with

slow acetylators at increased risk (Clark, 1985). Accordingly, an association with bladder cancer has been the subject of a large number of studies, recently reviewed by Hein (Hein, 1988). Collectively, these studies comprise 981 cancer cases and 1244 controls, and the odds ratio for bladder cancer among slow acetylators can be calculated to 1.5 (95% CI: 1.2-1.7). The arylamine bladder carcinogenesis has been reproduced in several relevant animal models of the acetylator polymorphism (Juberg et al.,1991).

With respect to heterocyclic amines, e.g. cooked food mutagens, O-acetylation after CYP1A2 catalyzed N-hydroxylation in the liver is a toxification process forming the proximate carcinogen. The proximate carcinogens can be transported as glucuronide conjugate via the bile to the colon and liberated by hydrolysis by bacteria. In accordance, fast acetylators have been shown to be at increased risk of colon cancer in three studies (Ilett et al.,1987; Lang et al.,1986; Wohlleb et al.,1990). The collective odds ratio of colon cancer in fast acetylators calculated from the first two studies involving a total of 92 cases and 82 controls was 3.3 (95% CI: 1.7-6.3), (Loft, 1990). In the third study (Wohlleb et al.,1990) the odds ratio was 2.48 (1.02-6.03). However, in a fourth study (Ladero et al.,1991) the frequency of fast acetylators was 55% among 109 colon cancer patients compared to 58% among controls, i.e. not different.

Thus, the epidemiologic support of an association between the acetylation polymorphism and colon cancer is not strong. Several heterocyclic amines have been shown to induce colon cancer in rodents, although the polymorphism so far is untested in this respect.

Breast cancer has been investigated with the hypothesis that fast acetylators are at increased risk. However, three studies, including one involving 410 cases and 377 healthy subjects as controls, have failed to show significant differences in acetylator frequency (Philip et al.,1987b; Ladero et al.,1987). Likewise, no signs were found of associations between the acetylator polymorphism and the risk of lung cancer (Roots et al.,1988; Philip et al.,1988) or malignant lymphoma (Philip et al.,1987a). A relative risk of gastric cancer of 1.79 in slow acetylators has been published in an abstract of a study involving 124 cases and 155 controls, however, the paper is devoid of details regarding the statistics (Roots et al.,1986).

The conclusion on the acetylator polymorphism and cancer risk is at present that there is strong epidemiological evidence of an increased risk of bladder cancer in slow acetylators, particularly those occupationally exposed to arylamines. The evidence is weaker concerning the increased colon cancer risk in fast acetylators. Both hypotheses are supported by *in vitro* and animal data.

Glutathione-S-Transferases(GSTs) polymorphism.
The GSTs are a family of enzymes which catalyze conjugation of electrophilic intermediates with the tripeptide glutathione, producing hydrophilic compounds that are excreted readily into urine. It is therefore of particular interest in relation to a variety of potential carcinogens, e.g. polycyclic aromatic hydrocarbons from tobacco smoke or other origins. GSTs are classified into three forms based on the isoelectric point (Mannervik et al.,1985). For the Mu form (the near-neutral GST1 0) it has been demonstrated that about 50% of the caucasian population fail to express the activity in liver or leukocytes (Seidegaard et al.,1986). The trait is a genetic polymorphism in both alleles (Seidegaard et al.,1988).

The work by Seidegaard et al. (1986, 1990) on 125 lung cancer patients demonstrated that the GST Mu defect was significantly related to lung cancer risk. In a recent study on lung (n=66), oral (n=15), bladder (n=32), and prostate cancer (n=23) high GST Mu activity had a low odds ratio of 0.6, however, it did not reach statistical significance (95% CI: 0.3 - 1.1) (Heckbert et al.,1992). Also in another small series of 49 lung cancer cases a relation to the Mu defect was not indicated (Brockmoller et al.,1991), but without further details.

A significant odds ratio of 3.0 (95% confidence limits 1.6 - 6.0) was found in a study on adenocarcinoma of the stomach and the colon, which included a total of 45 cases versus 148 controls of various ethnic origins (Strange et al.,1991). In another study on polyposis coli and colon cancer (n=52) no importance of the Mu defect could be identified (Peters et al.,1990). The latter study also included a group of 52 patients with breast cancer which was found to be unrelated to the Mu defect.

The conclusion on glutathione-S-transferase Mu defect and cancer risk is presently that there is conflicting epidemiological evidence concerning increased lung cancer risk in smokers, and some epidemiological evidence for a relation between adenocarcinoma of the gastrointestinal tract and the Mu defect.

CYP2E1 restriction fragment length polymorphism.
CYP2E1 is responsible for the activation of nitrosamine to proximate and ultimate carcinogens. Recently, an RFLP of CYP2E1, involving the restriction enzyme *DraI*, was reported to be associated with lung cancer in a Japanese population (Uematsu et al.,1991). Of 47 lung cases none were homozygous for a 5.5 kb fragment as opposed to 6 among the 56 controls. So far this RFLP has not been linked to expression or activity of CYP2E1 and even if the suggested association is verified it may not be causal, but merely a marker of another genetic risk factor.

Phenol sulfotransferase polymorphism.
These enzymes are much less studied than e.g. the cytochrome P450 enzymes. Thermal stability of the enzyme in platelets has been demonstrated and indicate differences in protein structure. The thermal stability of hepatic sulfotransferase from humans showed that 11% had low, 36% had intermediate and 53% had high thermal stability (Weinshilboum, 1990). This is indicative of a genetic polymorphism. The molecular details and relation to diseases, e.g. cancer remains obscure, but the sulfation is such an important detoxification route for many xenobiotics that the polymorphism indicates further investigations of the relation of the defect to disease.

The conclusion on phenol sulfotrasferase is that there is no epidemiological evidence relating the polymorphism to disease risk.

Methyl conjugation polymorphism.
Thiol methylation is an important pathway in the metabolism of many sulfhydryl xenobiotics, e.g. D-penicillamine and 6-mercaptopurine. Four isoenzymes in cytosol and in membranes are identified. The thiopurine methyltransferase in red blood cells is polymorphically distributed, 0.3% had undetectable activity, 11.1% intermediate activity and 88.6% had high activity, in agreement with a single gene regulation from two alleles, one for low (frequency 6%) and one for high activity (frequency 94%). The catechol O-methyltransferase is a similar balanced genetic polymorphism where about 25% are homozygous and have high activities. Drug toxicity occurs more frequently in slow metabolizers (Weinshilboum, 1989).

At present there is no epidemiological evidence relating thiol methylation to diseases risk.

Sulfoxidation polymorphism.
The capacity for the cytosolic sulfoxidation of S-carboxy-L-methylcysteine as assessed by its urinary metabolic ratio was bimodally distributed in the population suggesting genetic control (Mitchell et al.,1984; Waring et al.,1986). Moreover, poor sulfoxidizers of this probe have been reported to be more prone to penicillamine toxicity and to various central nervous system diseases and allergies, possibly attributed to exposure to foreign compounds (Emery et al.,1984; Steventon et al.,1988; Scadding et al.,1988; Olumo et al.,1988). Whether sulfoxidation truly is a polymorphism is, however, debated (Meese et al.,1991).

DNA Repair Polymorphisms and Cancer Risk.

The mammalian DNA repair processes appear to be of considerable complexity. They are regulated by many genes and there are many different repair pathways depending upon the type of damage, and, as has become evident lately, also upon its precise location in the genome. Interindividual differences in DNA repair capacity may contribute to variability in genetic susceptibility to cancer. Individuals suffering from genetic disorders in which DNA repair is defective are known to be at elevated risk for certain types of cancer as illustrated in Table 1 (see (Hanawalt & Sarasin, 1986) for review). Heterozygous carriers of the mutant alleles of these disorders may also have increased vulnerability because of suboptimal levels of repair. The goal of understanding the biochemical details of specific repair pathways is made difficult by their genetic complexity combined with the likely low abundance of many repair proteins. Yet, recently some insights have developed toward this goal.

A number of repair genes have been localized on specific human chromosomes (Table 2). One of the primary reasons for making these chromosome assignments is that the locations provide a way of distinguishing different genes. Generally, repair-deficiency mutations have been classified into genetic complementation groups by making cell hybrids. In the case of sensitivity to ultraviolet (UV) light mutations many complementation groups have been identified from both xeroderma pigmentosum (XP) patients and rodent cells in culture. Thus, classical XP mutants fall into eight or nine complementation groups (Fischer et

Table 1.

Human hereditary disorders with hypersensitivity to DNA damage.

Disorder	Increased Risk of Cancer
Established DNA repair deficiency:	
Xeroderma pigmentosum	Yes
Cockayne's syndrome	No
Bloom's syndrome	Yes
Likely DNA repair defect:	
Fanconi's anemia	Yes
Ataxia telangiectasia	Yes
Suspected DNA repair defect:	
Nevoid basal cell carcinoma	Yes
Gardner's syndrome	Yes
Dyskeratosis congenita	Yes
Tricothiodystrophy	No

The information in this table is taken from (Bohr et al., 1989)

Table 2.

Human DNA repair genes.

Repair gene	Human chromosome assignment	Cloned
ERCC-1	19	yes
ERCC-2	19	yes
ERCC-3	2	partly
ERCC-4	16	no
ERCC-5	13	yes
ERCC-6	ND	partly
XRCC-1	19	yes
XRCC-2	7	no

al.,1985; Johnson et al.,1989), suggesting that eight or nine genes may be involved in damage recognition and incision in this human syndrome. Cells from patients with the classical XP are defective in performing the incision step of nucleotide excision repair (Cleaver, 1983).

The *ERCC1-ERCC6* (excision repair cross-complementing) genes are involved in the nucleotide excision repair pathway that usually operates on DNA lesions such as bulky DNA adducts from a number of chemicals and photoproducts from UV-light radiation. These genes correspond to the first 6 of 8 complementation groups of UV-sensitive rodent mutants identified so far (Thompson et al.,1988). The first 5 rodent complementation groups are, like XP, defective in the incision step (Thompson et al.,1982b), while the sixth group has a defect in the removal of UV induced pyrimidine dimers but not (6-4)-photoproducts (Thompson et al.,1989). Both *ERCC1* and *ERCC2* have been localized to within 250 kb of each other on the same chromosome (Mohrenweiser et al.,1989). Whether this linkage has any functional significance is unclear since other chromosomally assigned *ERCC* genes are located on different chromosomes.

The human *ERCC1* gene restores the sensitivity to UV and mitomycin C of excision deficient Chinese hamster ovary mutant cells of complementation group 1 to almost wild-type levels (Westerveld et al.,1984; Zdzienicka et al.,1987). Also, *ERCC1* has been shown to restore the preferential repair of UV-induced pyrimidine dimers in the *DHFR* gene (Bohr et al.,1988). The gene is unlikely to be involved in any of the known excision repair disorders XP and Cockayne's syndrome (van Duin et al.,1989). This may not be unexpected as the rodent complementation group 1 exhibits extreme sensitivity to cross-linking agents such as mitomycin C and cisplatin (Parker et al.,1990), a characteristic associated with Fanconi anemia cells rather than XP. Rodent complementation groups 2, 3 and 5 closely parallel XP cells phenotypically.

The *XRCC1* and *XRCC2* (X-ray repair cross-complementing) genes are involved in aspects of DNA repair other than the nucleotide excision repair pathway. These genes have the common property of providing an enhancement of resistance to ionizing radiation when present on the complementing human chromosome in hybrids of the corresponding rodent cell mutant. Yet, the hypersensitivity of these mutants is not restricted to ionizing radiation. Ionizing radiation produces a wide spectrum of DNA lesions, which are repaired primarily by AP endonucleases and glycosylases. As such, one may expect cells corrected by the cloned *XRCC* genes to be highly sensitive to radiomimetic agents and certain alkylating chemicals. Thus, rodent cells, which were corrected by the cloned *XRCC1* gene and *XRCC2* gene, exhibited extreme hypersensitivity to ethyl methanesulfonate (Thompson et al.,1982a) and mitomycin C (Jones et al.,1987), respectively. In the human disorder ataxia telangiectasia (AT) cells, the cells in culture are noted for their hypersensitivity to killing by ionizing radiation but also a characteristic resistance to radiation-mediated inhibition of DNA synthesis (Painter & Young, 1980). AT cells probably fall into several complementation groups. The AT group A gene has recently been reported to be located on the human chromosome 11 (Gatti et al.,1988). No definitive defect in DNA repair has been established in this human syndrome.

Over the past decade a significant advance in biochemical technology has improved the recognition of DNA repair deficiency in some human syndromes particularly susceptible to cancer. A better understanding of the pathomechanism of these diseases opens new perspectives for diagnosis and treatment of a number of disorders. As such, one may speculate in gene therapy with DNA repair genes which could be a causal therapy for many individuals. Furthermore, an early assessment of DNA repair efficiency may lead to important information with respect to cancer risk and prevention.

The conclusion on the DNA repair deficiency in certain human disorders and cancer risk is supported by both clinical and epidemiological studies. Yet, there is no unambiguous epidemiological evidence available for cancer risk in general. *In vivo* methods have to be refined and developed, for use in epidemiological studies.

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