Interaction between Dose and Susceptibility to Environmental Cancer: A Short Review

Eino Hietanen,1 Kirsti Husgafvel-Pursiainen,2 and Harri Vainio2

1Department of Clinical Physiology, University of Turku, Turku, Finland; 2Institute of Occupational Health, Toepeliuksen, Helsinki, Finland

Increased risk of environmentally induced cancer is associated with various types of exposures and host factors, including differences in carcinogen metabolism. Since many carcinogenic compounds require metabolic activation to enable them to react with cellular macromolecules, individual features of carcinogen metabolism may play an essential role in the development of environmental cancer. In this context, cigarette smoking has often been the main type of carcinogenic exposure examined in human studies. Increasing attention has recently been paid to the dose level at which individual susceptibility may be observed. Present studies on increased risk of smoking-related lung cancer associated with phenotypic or genotypic variation of the genes encoding for CYP1A1 or CYP2D6 enzymes are summarized. Similarly, higher risks of lung or bladder cancer seen at various levels of smoking in association with polymorphism of the glutathione S-transferase gene GSTM1 or NAT1 and NAT2 genes involved in N-acetylation are reviewed. Finally, the influence of CYP2E1, GSTM1, or the combined at-risk genotype on the risk of hepatocellular carcinoma in smokers is briefly discussed. — Environ Health Perspect 105(Suppl 4):749–754 (1997)

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Introduction

Increased risk of cancer and other environmentally induced diseases is associated with various types of exposures and host factors, including differences in carcinogen metabolism. Since many carcinogenic compounds require metabolic activation before they can react with cellular macromolecules, individual features of carcinogen metabolism may play an essential role in the development of environmental cancer (1). Many compounds are converted to reactive electrophilic metabolites by the oxidative, mainly cytochrome P450-related enzymes (CYPs). Secondary metabolism, mainly involving epoxide hydrolyase and another subset of activating CYP isoforms, leads to the formation of the highly reactive metabolites that can bind to genomic DNA (2). Other enzyme systems, e.g., many transferases such as glutathione S-transferases, UDP-glucuronosyltransferases, sulfotransferases, and acetyltransferases, take part in detoxification of oxidated forms of carcinogens. Thus, the concerted action of these enzymes may be crucial in determining the final biological effect(s) of a xenobiotic chemical. A number of genes that encode carcinogen-metabolizing enzymes is presently known. Individual variation in enzymes activating or detoxifying carcinogens and other xenobiotics have subsequently been related to discovered genetic polymorphisms for these genes (1).

Recently, increasing attention has been paid to the dose level of exposure at which individual susceptibility may be observed (3). In this context, cigarette smoking is the main type of carcinogenic exposure examined in many human studies. Although it is well known that the risks for tobacco-related cancers increase with increased smoking (4) and that the composition and filter type of cigarettes modifies the risk (4), few studies have focused on possible dose dependence of cancer susceptibility.

The possible role of genetic factors in the regulation of the dose–response relationship after exposure to carcinogens has been seen in animal studies. A difference related to genotype in formation of 2-aminofluorene–hemoglobin adducts was found in hamsters between slow and rapid acetylators; adduct formation increased more with dose in slow than in rapid acetylators (5). Similarly, formation of 4-aminobiphenyl–DNA adducts in mice was increased with dose in the liver and urinary bladder, but the effect appeared to be sex- and organ-specific (6).

Pulmonary Carcinogenesis

Inducibility of CYP1A1-related phenotypic activity can be regarded as an indirect quantitative measurement of effects related to dose and host factors. In the lungs an implication of this is the decreased level of inducibility found in lung cancer dependent on the time period patients refrained from smoking, while in noncancer patients no cigarette smoke-related inducibility could be demonstrated (7). Inducibility of CYP1A1 phenotype was first demonstrated by Kellermann et al. (8) to be higher in lung cancer patients than in controls. This association has also been shown using CYP1A1 activity in cryopreserved lymphocyte as the marker (9). Since these studies, association of CYP1A1 genotype with inducibility and lung cancer risk has been extensively studied (10–19). Anttila et al. (20) demonstrated the presence of CYP1A1 isozyme in the lung tissue of smokers with peripheral lung cancer. In the Japanese population, associations between risk of lung cancer and certain CYP1A1 alleles have been demonstrated in smokers (14–16); the association has not been confirmed in Caucasian populations, probably due to more infrequent occurrence of the at-risk allele in Caucasians (17,18,21,22). Possible dose dependence of CYP1A1-associated metabolic susceptibility has not been much examined. One of the first reports was a Japanese study (23) that observed that patients with the at-risk MspI CYP1A1 genotype (m2m2) contracted cancer after fewer cigarettes (mean lifetime consumption 31 ± 12 × 104 cigarettes) than those with other genotypes (mean lifetime consumption 43 ± 18 × 104 cigarettes). The individuals with the susceptible genotype were then found to have a high...
risk (OR 7.3, 95% CI 2.1–25) at a low dose level and the difference in susceptibility between the genotypes was reduced at high dose levels (23). In a later report (24), the finding of increased lung cancer risk associated with the \( Msp1 \) \( CYPIA1 \) susceptible genotype was confirmed; an excess risk was seen particularly in light smokers (less than \( 30 \times 10^9 \) cigarettes over lifetime) with squamous cell carcinoma as contrasted to those who had smoked more. In adenocarcinoma, no such relationship was found (Table 1). A recent study among African Americans (25) observed no overall association between lung cancer and a rare race-specific \( CYPIA1 \) polymorphism, although a slightly increased but nonsignificant risk was associated with the presence of the variant \( CYPIA1 \) allele at higher smoking level (1–35 pack-years, OR 1.3, 95% CI 0.6–3.2; >35, OR 2.2, 95% CI 0.6–7.8). Taken together these results appear to emphasize the influence of different allele frequencies in different human populations on risk experienced.

In genotyping studies using polymerase chain reaction assays (26,27), a tendency for an association between the \( GSTM1 \) genotype and squamous cell carcinoma has been reported (26,28,29). A Japanese study combining the risk genotypes for \( CYPIA1 \) and glutathione S-transferase 1 (\( GSTM1 \)) demonstrated an enhanced risk of lung cancer (30). Patients with the at-risk \( Msp1 \) or \( Ile-Val \) genotypes of \( CYPIA1 \) contracted lung cancer after smoking fewer cigarettes than those with the other \( CYPIA1 \) genotypes. In combined genotyping, the individuals with the susceptible genotype of \( CYPIA1 \) (\( Msp1 \)) and the \( GSTM1 \) null genotype were at a high risk with an odds ratio of 16.0 (95% CI 3.8–68) at the lower cumulative cigarette dose level (32 \( \times 10^4 \) cigarettes over lifetime) as compared to those with the other \( CYPIA1 \) genotypes and \( GSTM1^+ \) genotype. The risk estimate for the combined \( Val-Val \) \( CYPIA1 \) and \( GSTM1^+ \) genotype was even higher (OR 41, 95% CI 8.7–193) at the lower dose level (30). Similarly in another study, the \( GSTM1 \) null genotype was associated with an overall increased lung cancer risk (OR 1.87) (31). The study found a higher risk at the highest cumulative dose of cigarette smoke exposure in squamous cell carcinoma patients with \( GSTM1 \) null genotype; the odds ratio however, remained nonsignificant or at borderline significance (Table 2).

Association between some of the biomarkers related to initiation of carcinogenesis and susceptible genotypes has been noticed. Formation of smoking-related DNA adducts in human lung tissue can be used as a marker of internal dose, and smokers are known to have significantly elevated levels of aromatic and/or hydrophobic adducts compared with nonsmokers (32,33). In recent studies, up to 6-fold increase in the amount of pulmonary DNA adducts has been found in smokers as compared to ex-smokers or nonsmokers, with a tendency of \( GSTM1 \) null genotype individuals to have higher levels of adducts than those with at least one allele present (34).

Several studies have suggested that the capability to metabolize debrisoquine (a test drug) extensively (extensive metabolizers, EM) is associated with increased risk of lung cancer, as compared to poor metabolizers (PM) (35). A weak association between \( CYP2D6 \) genotype predictive of the EM phenotype and increased risk of lung cancer has since been reported by some studies, but other studies found no association (36–41). Recently, a positive association between the frequency of poor metabolizers and the risk of adenocarcinoma of the lungs was published (42). The association of PM genotype of \( CYP2D6 \) with increased risk of lung adenocarcinoma was speculated to be due to metabolic activity by this isozyme, a tobacco-specific nitrosamine 4-(methylnitrosamo)-1-(3-pyridyl)-1-butanoate (NNK), as also suggested by others (43). Present evidence for interaction between the risk related to \( CYP2D6 \) genotype/phenotype and the extent of smoking is difficult to evaluate because most studies lack quantitative data on smoking. Bouchardy et al. (44) observed an increased risk of lung cancer for extensive metabolizers. The excess risk in EMs was dependent on the level of smoking, while in individuals who were poor or intermediate metabolizers, no such increase was found even at high level of smoking (Table 3). The increased risk (OR 4.95) in extensive metabolizers became evident at the tobacco consumption level of >30 g/day as compared to smokers who consumed <20 g/day. This was again speculated to be associated with the increasing levels of metabolites of the tobacco-specific carcinogen NNK present in extensive metabolizers (44).

Occupational exposure to asbestos increases the risk of lung cancer and mesothelioma. Indications of increased risk of asbestos-related mesothelioma and other pulmonary disorders have been obtained recently. Both \( GSTM1 \) and \( NAT2 \) (N-acetylation) genotypes were associated with malignant mesothelioma in workers who were highly exposed to asbestos (45). In another study, \( GSTM1 \) null genotype was found to be related to risk of asbestosis (pulmonary fibrosis) among workers exposed to high levels of asbestos (46), whereas no association between radiographic or lung function changes and \( GSTM1 \) genotype was seen in a group of asbestos workers with mostly low or moderate exposure (47). Glutathione S-transferase

| Table 1. \( CYPIA1 \) (\( Msp1 \)) genotype and exposure to cigarette smoke. |
|-----------------|-----------------|-----------------|
| Genotype       | \( m1m1 \) | \( m1m2 \) | \( m2m2 \) |
| Adenocarcinoma  | 11 | 33 | 6 |
| \( n = 41 \)   | 0 | 34 | 21 |
| <30            | 0 | 26 | 57 |
| >30            | 0 | 42 | 47 |
| Total          | 35 | 53 | 13 |
| Squamous cell carcinoma  | 11 | 33 | 6 |
| \( n = 78 \)   | 0 | 100 | 0 |
| <30            | 0 | 28 | 38 |
| >30            | 0 | 44 | 44 |
| Total          | 40 | 40 | 21 |
| All patients   | 11 | 33 | 6 |
| \( n = 250 \)  | 36 | 47 | 16 |
| Historical healthy controls  | 11 | 33 | 6 |
| \( n = 166 \)  | 44 | 45 | 11 |

The number of cigarettes given refers to the amount consumed over a lifetime smoking \( (\times 10^9) \). Modified from Okada et al. (24).

| Table 2. Association of \( GSTM1 \) null genotype and cumulative lifetime smoking in lung cancer patients by tumor histology. |
|-----------------|-----------------|-----------------|
| Type of cancer  | \( <40 \) | \( 40-60 \) | \( >60 \) |
| \( OR \)         | \( 95\% CI \)   | \( OR \)         | \( 95\% CI \)   | \( OR \)         | \( 95\% CI \)   |
| Squamous cell carcinoma  | 1.22 | 0.36–4.14 | 1.49 | 0.53–4.22 | 3.18 | 0.98–10.9 |
| \( n = 7 \)    | (11) | (11) | (13) | (13) | (13) | (13) |
| Small cell carcinoma  | 0.87 | 0.23–3.26 | 2.44 | 0.72–8.73 | 3.66 | 0.64–27.3 |
| \( n = 5 \)    | (19) | (19) | (13) | (13) | (13) | (13) |
| Adenocarcinoma  | 1.32 | 0.54–3.24 | 1.49 | 0.53–4.22 | 1.22 | 0.33–4.55 |
| \( n = 14 \)   | (11) | (11) | (11) | (11) | (11) | (11) |

Abbreviations: OR, odds ratio; CI, confidence interval. Modified from Kihara et al. (37). Number of cases studied in parentheses.
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Table 3. CYP2D6 phenotypes and daily tobacco consumption in lung cancer patients.a

| Tobacco consumption, g/day | Phenotypic CYP2D6 classification (n=19) | Low OR | 95% CI | Medium OR | 95% CI | High OR | 95% CI |
|---------------------------|----------------------------------------|--------|--------|-----------|--------|---------|--------|
| <20                       | 1.0 (26/17)                            | 1.0    |        | 1.0       |        |
| 21–30                     | 0.43 (8/16)                            | 0.14–0.37 | 1.04    | 0.30–3.60 | 1.43   | 0.42–4.85 |
| >30                       | 0.40 (12/18)                           | 0.13–1.15 | 0.43    | 0.14–1.34 | 4.95   | 1.61–15.23 |

Abbreviations: OR, odds ratio; CI, confidence interval. aModified from Bouchardy et al. (44). *Number of subjects studied in parentheses (cases/controls).

Table 4. Effect of NAT2 acetylator phenotype on the level of aminobiphenyl-hemoglobin adducts at different levels of cigarette smoke exposure.a

| Urinary nicotine + cotinine, µmol/mmol creatinine | NAT2 acetylator phenotype | % Increase in adducts |
|--------------------------------------------------|--------------------------|-----------------------|
| 0 (n=44)                                         | Rapid, ABP-Hb, pg/g Hb   | 13                    | 27                    | 107 |
| 0.5 (n=25)                                       | Slow, ABP-Hb, pg/g Hb    | 52                    | 99                    | 90  |
| 1.5–2.4 (n=9)                                    |                          | 92                    | 132                   | 43  |
| 2.5 (n=19)                                       |                          | 128                   | 119                   | –7  |

Modified from Vineis et al. (51). aDetermined by urinary nicotine + cotinine concentration. bNumber of subjects studied in parentheses.

isozymes take part in reactions detoxifying reactive oxygen species (48), known to be generated by asbestos exposure and smoking. The excess risk associated with GSTM1 null genotype in the asbestos-exposed patients in these studies appeared, however, to be exerted at a high level of exposure only. The possible mechanistic role of N-acetylation genotype in modifying risk for asbestos-related malignant mesothelioma is more difficult to see.

Bladder Carcinogens and Bladder Cancer

Malaveille et al. (49) found a dose-dependent relationship between urinary mutagenicity, amount of thioethers, and the number of cigarettes smoked per day as well as the amount of nicotine and cotinine in urine. Furthermore, the mutagenicity was nearly twice as high in dose-corrected black tobacco smokers than in blond tobacco smokers. Bartsch et al. (50) showed a dose-dependence of ABP aminobiphenyl-hemoglobin (ABP–Hb) adducts and the concentration of cotinine + nicotine in urine, but no clear-cut quantitative association could be shown between the amount of adducts and the amount of smoking. Later, a dose-dependent increase in ABP–Hb adducts was demonstrated (51).

Furthermore, the amount of adducts was higher in slow than in rapid N-acetylators (determined both genotypically and phenotypically) at low dose levels (as judged by urinary cotinine + nicotine levels), but at higher dose levels the difference tended to level off (Table 4). The difference in acetylation phenotype was also reflected in the presence of DNA adducts to aminobiphenyl metabolites in urothelial cells, and the amount of adducts increased with increasing urinary mutagenicity. However, within the same genotype no correlation between the acetylation rate as assayed by caffeine metabolites was found (51).

Aspects related to dose might be important in evaluating the postulated modulation of bladder cancer risk by metabolic polymorphisms, e.g., those for NAT2 or GSTM1 (52–56). In the study by Bell et al. (57), an increase in risk of bladder cancer was found for patients with the GSTM1 null genotype than for those who were homozygous or heterozygous for the GSTM1 wild-type allele. No significant relationship with dose could be seen, although some difference between smoking levels was observed (<50 pack-years vs. >50 pack-years; Table 5). Brockmoller et al. (58), who found an overall 1.40-fold increased risk of bladder cancer associated with GSTM1 null genotype, did not find dependence of the risk on increasing amount of smoking; in contrast, the risk appeared to be associated with lower dose level. In keeping with other studies, both NAT1 and NAT2 enzymes catalyze the activation (O-acetylation) and inactivation (N-acetylation) of alylamine carcinogens. Polymorphism in acetylation rate was first associated with NAT2 gene locus, NAT2 (59). In a study on occupational exposure to bladder carcinogens, low acetylation rate was observed to offer moderate protection from bladder cancer in benzidine-exposed workers (54). Cigarette smoking appeared to influence the risk, with a somewhat higher estimate for higher level of smoking (<20 pack-years, OR 1.4; >20 pack-years, OR 1.6).

Other Malignancies

Risk of hepatocellular carcinoma (HCC) was studied in a Taiwanese population, most of whom were also positive for hepatitis-B antigen (60). In this study, the significance of cytochrome P450E and GSTM1 genotypes was examined. An increase in the HCC risk was reported to occur depending on the dose of cigarette smoke exposure in patients who were homozygous for the e1 allele (e1/e1) of the CYP2E1 gene. No association with GSTM1 null genotype was found (Tables 6, 7). Defective alleles of the CYP2D6 gene may also be involved in increased risk of liver cancer; subjects having functional gene (extensive metabolizer genotypes) seemed to have 6.4-fold higher risk of primary liver cancer than those who had defective alleles (61). Possible hepatocarcinogens involved in or
Table 6. CYP2E1 (Pst1) and GSTM1 at-risk genotypes in hepatocellular carcinoma patients by cumulative lifetime smoking

| Smoking, pack-years | CYP2E1 c/c1 | GSTM1 null |
|---------------------|-------------|------------|
| Nonsmokers          | 1.0 (12/66) | 1.0 (10/61) |
| Smokers             |             |            |
| 1-17.4              | 1.8 (15/15) | 1.1 (3/16) |
| 17.5-29.2           | 3.1 (14/7)  | 0.8 (1/8)  |
| >29.2               | 3.7 (14/6)  | 1.2 (2/10) |

Abbreviations: OR, odds ratio; CI, confidence interval. *Modified from Yu et al. (60). **Number of cases in parentheses.

Table 7. CYP2E1 (Pst1) at-risk genotype, alcohol consumption and cigarette smoking in hepatocellular carcinoma patients.

| Alcohol | Cigarette smoking | CYP2E1 c/c1 | OR 95% CI | Subjects studied, cases/controls |
|---------|------------------|-------------|-----------|---------------------------------|
| No      | No               | No          | 1.0       | 5/55                            |
| No      | No               | Yes         | 2.1       | 0.7-6.4                         | 11/58 |
| Yes     | No               | Yes         | 1.4       | 0.1-13.3                        | 1/6   |
| No      | Yes              | Yes         | 3.9       | 1.1-13.5                        | 7/20  |
| Yes     | Yes              | Yes         | 7.3       | 1.8-29.2                        | 6/9   |

Abbreviations: OR, odds ratio; CI, confidence interval. *Modified from Yu et al. (60).

Table 8. GSTM1 genotype and smoking status in patients with colorectal adenoma.

| Smoking status | Subjects studied cases/controls | GSTM1+ | GSTM1 null |
|----------------|---------------------------------|--------|------------|
| Never smoked   | 166/209                         | 1.0    | 0.94       |
| Ex-smoker      | 190/217                         | 1.23   | 0.88-1.99  |
| Current smoker | 90/62                           | 1.73   | 2.07       |

Abbreviations: OR, odds ratio; CI, confidence interval. *Modified from Lin et al. (64).

metabolized by this cytochrome P450 isozyme are not known.

Another malignancy for which modification of risk by metabolic polymorphisms has been implied is colorectal cancer. Rapid acetylators (NAT2) may be at risk for colorectal cancers (62), although a study by Bell et al. (63) in a British population could not confirm this. Instead, an increased risk (OR 1.9) was found to be associated with NAT1*10 allele of the NAT1 gene, which encodes a different acetyltransferase isozyme (59). However, the increased risk associated with the NAT1 variant allele was most apparent in NAT2 rapid acetylators (OR 2.8), proposing a gene-to-gene interaction. Lin et al. (64), on the other hand, studied possible influence of GSTM1 on the risk of colorectal adenoma. They found that the risk was increased with smoking, but no association with GSTM1 genotype was found (Table 8).

Conclusions

Susceptibility to certain environmental cancers due to variation in xenobiotic metabolism has been demonstrated in many studies using either phenotyping or genotyping assays. Some of the studies, e.g., those on lung cancer, have reported conflicting results. It is only recently, and so far in relatively few studies, that influence of exposure levels or internal dose has been examined as a potential modifier of increased cancer risk linked to genetic susceptibility. Relationship between dose and increased metabolic susceptibility to cancer appears to vary from gene to gene, and with respect to combinations of genotypes as well as the organ under study (i.e., tissue specific expression of the isozymes). On the basis of present studies it can be speculated that in one tissue, increased susceptibility may become evident at low exposure doses while in the other this is seen at a high exposure dose only. Present knowledge does not allow a conclusion as to whether this hypothesized variation could be related to the overall capacity of the tissue to metabolize xenobiotics. In such a case, high exposure levels might saturate metabolic capacity by producing large quantities of reactive intermediates, while at low doses individual variations in metabolism might be more significant. Where the increased risk associated with susceptible genotypes is observed only at high doses, it could be that tissue-specific repair mechanisms would be efficient in protecting against carcinogenicity at low doses, thus masking possible influence of genetic susceptibility factors. It is also possible that other than host-related protective factors might be involved. For example, different dietary habits between populations could result in such a situation.

Another major point to be taken into consideration is the remarkable variation in metabolic phenotypes and genotypes reported for different ethnic or geographic populations (65-69). When comparing the influence of genetic susceptibility to lung cancer between ethnically different populations, e.g., Caucasians and Japanese populations, and taking smoking habits also into account, the results obtained vary greatly; in large part, this can be attributed to differences in distribution of the at-risk alleles in these populations. In a study by Caporaso et al. (35) in which extensive metabolizers of debrisoquine were found to be at 4.5- to 10.2-fold risk of lung cancer, a 2-fold difference between whites and blacks was observed. Epidemiologic studies have pointed to differences in smoking-associated lung cancer risk between various ethnic groups. In a Hawaiian study in which many confounding factors—e.g., smoking habits, pack-years of smoking, cancer histology, occupation, education, and dietary factors—were adjusted for, researchers observed a greater than 2-fold difference in cancer risk between Japanese and Hawaiian men (70).

In conclusion, the present data appear to support suggestions that increased susceptibility to environmental cancer due to phenotypic or genotype variation in carcinogen metabolism may be different at different levels of exposure, although other factors, internal or external, are likely to be involved also.

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