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Constitutive and Inducible Expression of Cytochromes P4501A (CYP1A1 and CYP1A2) in Normal Prostate and Prostate Cancer Cells

Kenneth M. Sterling, Jr.[1]* and Kenneth R. Cutroneo[2]

[1]University of Florida, Whitney Laboratory, 9505 Ocean Shore Blvd., St. Augustine, Florida 32080 and Dartmouth College, Department of Physics and Astronomy, 6127 Wilder Laboratory, Hanover, New Hampshire 03755-3528
[2]Department of Biochemistry, College of Medicine, University of Vermont, Burlington, Vermont 05405

Abstract Constitutive and benzo[*a*]pyrene (B[*a*]P) inducible expression of CYP1A1 and CYP1A2 in prostate cancer and normal prostate epithelial cells were examined by immunoblotting. Androgen independent prostate cancer cell lines DU145 and PC3 have constitutive expression of CYP1A and CYP1A1 and CYP1A2, respectively. Four micromolar B[*a*]P did not appear to induce CYP1A1 or CYP1A2 expression in DU145 or PC3 cells. The androgen dependent prostate cancer cell line, LnCap, also has constitutive expression of CYP1A1 and CYP1A2. However, both CYP1A1 and CYP1A2 are induced by treatment of LnCap cells with 4 μM B[*a*]P. Untreated normal prostate and primary prostate tumor cells have no detectable CYP1A1 expression. Treatment with 4 μM B[*a*]P induced CYP1A1 expression in both normal and primary tumor prostate cells. Constitutive CYP1A2 expression was detected in normal prostate cells with little or no induction by exposure to 4 μM B[*a*]P. Primary prostate tumor cells did not show constitutive expression of CYP1A2. However, CYP1A2 was induced by 4 μM B[*a*]P in primary prostate tumor cells. These observations indicate that hormonal and cancer specific factors affect the expression and induction of the phase I metabolic enzymes, CYP1A1 and CYP1A2 in prostate cells. These observations may be related to the potential smoking-linked higher risk of prostate cancer development and morbidity of prostate cancer patients who smoke. J. Cell. Biochem. 91: 423–429, 2004.

Key words: prostate cancer; B[*a*]P; PAH; dietary carcinogens; smoking; CYP1A

The cytochrome P450-dependent monooxygenases represent a large family of isozymes that catalyze the metabolic activation of protoxins, procarcinogens, and the detoxification of a multitude of environmental substrates [Conney, 1967, 1982; Nebert and Gonzalez, 1987]. The CYP1 subfamily includes CYP1A1, CYP1A2, and CYP1B1 [Morville et al., 1983; Thomas et al., 1983; Sutter et al., 1991]. Normally CYP1A1 expression is not constitutive in adult human tissues, however, its expression is highly induced by exposure to polyaromatic hydrocarbons (PAHs) and halogenated aromatic hydrocarbons found in tobacco smoke, environmental contaminants, and dietary constituents [Whitlock, 1986]. Expression of CYP1A1 is primarily under transcriptional control and involves the interaction of both positively and negatively acting transcription factors [Whitlock, 1986; Hines et al., 1988; Boucher et al., 1995; Sterling and Bresnick, 1996]. The level of induction of CYP1A1 also varies and a highly inducible phenotype is present in about 10% of the population [Kouri and Nebert, 1977; Fujino et al., 1984; Hayashi and Sugimura, 1994; Catteau et al., 1995]. Since CYP1A1 is a phase I activating enzyme that plays a major role in the conversion of procarcinogens to carcinogens such as benzo[*a*]pyrene (B[*a*]P) to B[*a*]P diol epoxide, it is believed that genetic differences (polymorphisms) that phenotypically show increased induction of CYP1A1 correlate with a predisposition to certain cancers [Kouri et al., 1982; Pelkonen and Nebert, 1982; Murray et al., 1991; Pyykko et al., 1991].

*Correspondence to: Kenneth M. Sterling, Jr., University of Florida, Whitney Laboratory, 9505 Ocean Shore Blvd., St. Augustine, FL 32080. E-mail: kms@whitney.ufl.edu

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CYP1A2 is also a phase I activating enzyme and is responsible for the activation of a number of aromatic amines, found in cooked foods, to carcinogenic forms [Battula et al., 1990; McManus et al., 1990]. CYP1A2 is the major CYP1A isozyme of the liver having a constitutive level of expression that is increased by exposure to aromatic amines, PAHs and dioxins [Battula et al., 1990; McManus et al., 1990; Murray et al., 1993]. CYP1A2 mRNA is also expressed in prostate tissue [Williams et al., 2000]. Based on studies of caffeine metabolism there are also inter-individual differences in the expression of CYP1A2 [Kalow and Tang, 1991; Kadlubar et al., 1992; Relling et al., 1992]. Higher levels of CYP1A2 expression or induction may contribute to individual susceptibility to cancer development from exposure to environmental and dietary precarcinogens. The underlying mechanism of the inter-individual variation in the level of CYP1A2 expression is not clear and does not appear to be due to mutations or deletions [Schweikl et al., 1993; Nakajima et al., 1994]. The inter-individual variation in the expression of CYP1A2 may be due to a differential response to various stimuli and/or unidentified polymorphisms present in the *CYP1A2* gene that occur in the population. An example of a differential response in the expression of CYP1A2 is its variable induction in response to cigarette smoke [Wrighton et al., 1986; Sesardic et al., 1990; Sherson et al., 1992; Vistisen et al., 1992, Ilett et al., 1993; Schweikl et al., 1993; Nakajima et al., 1994].

Prostate cancer is the second most frequent cause of male cancer deaths in the United States [Wingo et al., 1995]. Despite the prevalence of prostate cancer in the United States, little is known about its pathogenesis and the factors that contribute to its progression [Carter and Coffey, 1990]. There are significant differences in the incidence of prostate cancer throughout the world [Haenzel and Kurihara, 1968] and between ethnic groups [Ries et al., 1994]. This indicates genetic as well as environmental factors having a major etiological role in prostate cancer development. A potential target of the carcinogenic metabolites generated by the activity of CYP1As is the prostate specific tumor suppressor Nkx3.1 that plays a significant role in prostate development and cancer [Bhatia-Gaur et al., 1999; Abate-Shen et al., 2003].

An epidemiological report from a large prospective study indicated higher death rates due to prostate cancer for men who are cigarette smokers [Rodriguez et al., 1997]. Also, several other epidemiological studies have revealed a correlation between smoking and an increased risk of prostate cancer and mortality [Hsing et al., 1990, 1991; Andersson et al., 1996; Coughlin et al., 1996].

A potential role for CYP1A in the development and/or progression of prostate cancer is indicated by the significant amount of immunoreactive CYP1A observed in prostatic carcinomas, while non-neoplastic prostatic epithelium dislplayed weak immunoreactivity for CYP1A [Murray et al., 1995]. CYP1As were also shown to metabolize B[a]P with resultant formation of B[a]P adducts in benign prostatic hyperplasia organ cultures [Williams et al., 2000]. A preexisting polymorphism in the *CYP1A* genes, an aberrant level of expression of a positively acting CYP1A transcription factor or a cancer related switch to increased constitutive or induced levels of CYP1A expression, have the potential to explain, at the molecular level, the development and/or progression of prostate cancer from exposure to environmental precarcinogens. Increased morbidity of prostate cancer patients who smoke and the observed increased incidence of prostate cancer for smokers may be due to increased production of metabolically activated precarcinogens.

MATERIALS AND METHODS

Cell Culture

Two of the metastatic prostate carcinoma cells lines, PC3 and DU145, are androgen receptor negative while a third metastatic prostate carcinoma cell line, LNCaP expresses high levels of androgen receptor protein and mRNA [Tilley et al., 1990]. These cells were obtained from the American Type Culture Collection. We obtained normal human prostate and patient matched primary prostate tumor cell lines from Dr. Suzanne L. Topalian (Surgery Branch, National Cancer Institute). We have assessed one of the sets of patient matched cell lines, 1542-NPTX and 1542-CP3TX [Bright et al., 1997]. 1542-NPTX is derived from normal prostate epithelium and 1542-CP3TX is derived from primary prostate tumor [Bright et al., 1997].

DU145, PC3, and LNCaP cell lines were cultured in Dulbecco's modified Eagle's medium

90% with 10% fetal bovine serum. 1542-NPTX and 1542-CP3TX cells were grown in keratinocyte growth medium (GIBCO, Carlsbad, CA), 5% heat inactivated fetal calf serum. These cells were grown to approximately 90% confluency and then administered B[*a*]P, 4 μM final concentration or vehicle, dimethylsulfoxide (DMSO). The cells were cultured for a further 24 h. The cells were washed with ice cold phosphate buffered saline (PBS) and then scraped and transferred to a 15 ml culture tube, washed in PBS twice, and then placed in lysis buffer (0.5% nonidet P40, 150 mM NaCl, 50 mM Tris-HCl pH 7.5, and 0.5% sodium deoxycholate) plus protease inhibitors (1 mM EDTA, 20 μg/ml phenylmethylsulfonyl fluoride (PMFS), 20 μg/ml aprotinin, 5 μg/ml pepstatin A, and 5 μg/ml leupeptin) and sonicated on ice. A BCA protein assay (Pierce, Rockford, IL) was performed on each lysate.

Immunoblot Analysis

Total cell lysate (50 μg of total protein for control and B[*a*]P-exposed cells) was combined with an equal volume of 2× SDS-gel loading buffer (5% SDS, 125 mM Tris-HCl, pH 6.8, 25% glycerol, 0.0025% bromophenol blue, plus 2-mercaptoethanol) and separated by sodium dodecylsulfate, polyacrylamide gel electrophoresis (SDS–PAGE) [Laemmli, 1970]. The SDS–PAGE separated proteins were transferred to a polyvinylidene difluoride (PVDF) membrane for 20 min at 75 V in 10 mM CAPS, pH 11, 10% methanol. The membrane with transferred protein was blocked with 5% milk, Tris-buffered saline (TBS), followed by incubation with anti-P450c (recognizes both CYP1A1 and CYP1A2), CYP1A1 or CYP1A2 antibodies (gifts from Dr. Paul Thomas, Rutgers University) diluted in 5% milk, TBS. After further washing, the membrane was incubated with goat ant-rabbit IgG antibody conjugated to horseradish peroxidase (Pierce) for 1 h, washed and the protein signal developed using the Pierce SuperSignal West Pico Chemiluminescent Substrate kit (Pierce). The blot was stripped of primary and secondary antibodies with IgG elution buffer (Pierce). The stripped membrane was reprobed with rabbit polyclonal antibody to actin (Sigma, St. Louis, MO). Quantification of the specific CYP1A1 and CYP1A2 signals for constitutive and induced LnCap cells was determined by the number of pixels per unit area normalized with respect to the signal for actin (43 kD). Signal intensity is proportional to protein expression. The relative amount of specific signals was expressed as a ratio to that of actin. By including a determination of the amount of actin for each cell lysate sample, we can account for gel loading errors and possible differences in the amount of protein transferred to the PVDF membrane.

RESULTS

DU145 cells were probed with the rabbit polyclonal antibody to P450C that reacts with both CYP1A1 and CYP1A2. DU145 cells constitutively express either CYP1A1 or CYP1A2 (MW approximately 52 kDa) but apparently not both since only one signal is observed (Fig. 1). Administration of B[*a*]P apparently did not further induce either CYP1A1 or CYP1A2 in DU145 cells.

The PC3 cells constitutively express both CYP1A1 and CYP1A2 and there is no apparent induction of either isozyme after exposure to B[*a*]P (Fig. 2).

The LNCaP cells also constitutively express both CYP1A1 and CYP1A2 (Fig. 3). Unlike the DU145 and PC3 cells, exposure to B[*a*]P caused an increase in the amount of CYP1A1 and CYP1A2 in LNCaP cells as indicated by the intensity of the respective signals for each and comparison to the signal intensities for actin (Fig. 4).

Compared to the metastatic prostate carcinoma cell lines, the normal and primary tumor prostate cells, 1542-NPTX and 1542-CP3TX, have very little or no constitutive expression of CYP1A1 (Fig. 5). CYP1A1 expression was also inducible in the normal and primary tumor prostate cells (Fig. 5). CYP1A2 was expressed

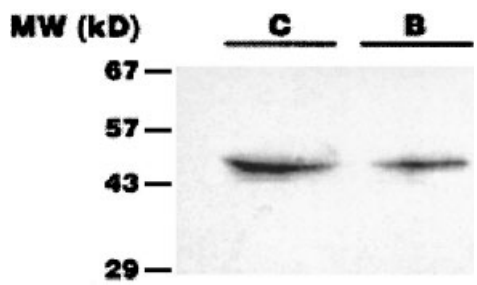

Fig. 1. DU145, androgen-independent prostate cancer cells were treated with vehicle (**lane C**) or 4 μM benzo[*a*]pyrene (B[*a*]P) (**lane B**). Fifty micrograms of total cell lysate protein was loaded in each lane. The transferred cellular protein was probed with a rabbit anti-human, cytochrome P450c antibody that recognizes both CYP1A1 and CYP1A2.

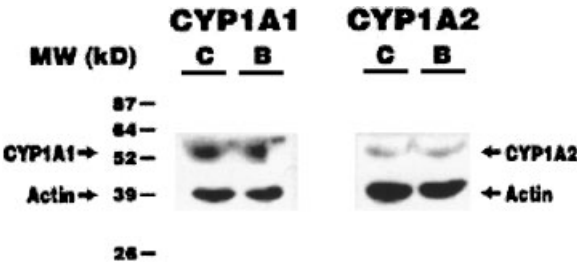

Fig. 2. PC3, androgen-independent prostate cancer cells were treated with vehicle (**lane C**) or 4 μM B[*a*]P (**lane B**). Fifty micrograms of total cell lysate protein was loaded in each lane. The transferred cellular protein was probed with either a rabbit anti-human, cytochrome P4501A1 or anti-human cytochrome P4501A2 (CYP1A1 and CYP1A2, respectively) antibody. Each immunoblot was stripped and re-probed with rabbit anti-actin antibody.

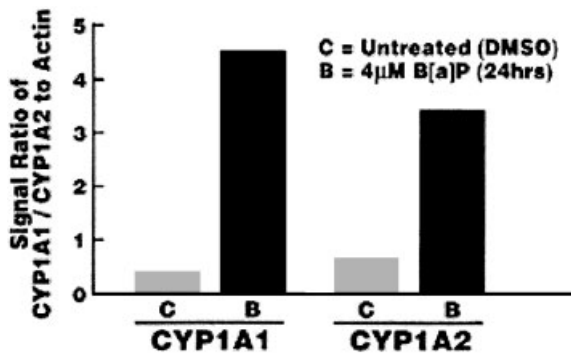

Fig. 4. Ratio of the CYP1A1 and CYP1A2 signal densities from control and B[*a*]P-treated LNCaP cells to their respective actin signal density from Figure 3.

constitutively and was apparently not increased by exposure to B[*a*]P in the normal prostate cells, 1542-NPTX (Fig. 5). CYP1A2 was not detected in the non-B[*a*]P-treated primary tumor prostate cells, 1542-CP3TX but was induced when the cells were exposed to 4 μM B[*a*]P.

DISCUSSION

Environmental precarcinogens, including those in tobacco smoke and the diet are believed to be responsible for most cancers. This report demonstrates that normal and patient matched primary tumor prostate cells did not have detectable levels of CYP1A1 expression. CYP1A2 expression was constitutive in normal prostate epithelial cells and not increased by B[*a*]P exposure. Primary prostate tumor cells had no constitutive expression of CYP1A2, however, B[*a*]P exposure caused increased expression of CYP1A2. All the metastatic prostate cancer cell lines, DU145, PC3, and LnCap showed constitutive expression of CYP1A1 and CYP1A2. CYP1A1 and CYP1A2 were not induced by exposure to B[*a*]P in the androgen-independent prostate cancer cell lines DU145 and PC3. However, CYP1A1 and CYP1B1 expression was induced only in high passage PC3 and DU145 cells exposed to 2,3,7,8-tetrchlorodibenzo-*p*-dioxin (TCDD) [Schaufler et al., 2002]. B[*a*]P exposure to the androgen-dependent prostate cancer cell line, LNCaP, caused an induction of CYP1A1 and CYP1A2 expression. These observations indicate that constitutive and induced expression of CYP1A varies according to whether the prostate cells are normal, primary, or metastatic and androgen dependent. This observation is in agreement with a previous report of TCDD induction of CYP1A1 mRNA in LnCap cells [Jana et al., 1999]. Both PAH's (e.g., B[*a*]P) and TCDD are ligands for the aromatic (aryl) hydrocarbon receptor (AhR) [Whitlock, 1999]. TCDD and testosterone signaling pathways apparently interact in LNCaP cells [Jana et al., 1999]. Thus, TCDD and other carcinogenic AhR ligands, e.g., B[*a*]P [Kizu et al., 2003], may contribute to the development and progression of prostate cancer via an endocrine pathway in addition to the action of their ultimate carcinogenic metabolites. These data provide the basis for further investigation of the mechanisms and genetic alterations responsible for the observed differences in CYP1A expression and induction in the various prostate cancer and normal prostate cells. Functional alterations in protein products of genetic targets, e.g., the prostate-

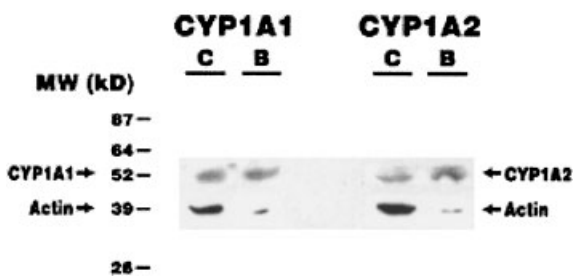

Fig. 3. LNCaP, androgen-dependent prostate cancer cells were treated with vehicle (**lane C**) or 4 μM B[*a*]P (**lane B**). Fifty micrograms of total cell lysate protein was loaded in each lane. The transferred cellular protein was probed with either a rabbit anti-human, cytochrome P4501A1 or anti-human cytochrome P4501A2 (CYP1A1 and CYP1A2, respectively) antibody. Each immunoblot was stripped and re-probed with rabbit anti-actin antibody.

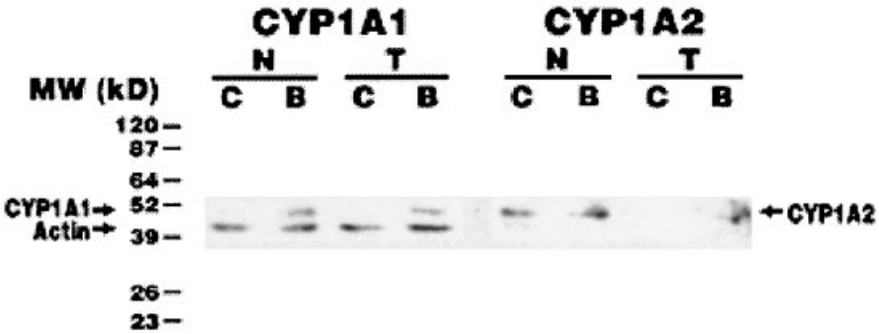

Fig. 5. Human, 1542-NPTX, normal (N) and 1542-CP3TX, primary tumor (T) prostate cancer cells were treated with vehicle (**lane C**) or 4 μM B[*a*]P (**lane B**). Twenty five micrograms of total cell lysate protein was loaded in each lane. The transferred cellular protein from each cell and treatment type was simultaneously probed with rabbit anti-human, cytochrome P4501A1 (CYP1A1) and rabbit anti-actin antibodies, **left panel**. The immunoblot was stripped and re-probed with anti-human, cytochrome P4501A2 (CYP1A2) antibody, **right panel**.

specific *Nkx3.1* gene [Bhatia-Gaur et al., 1999; Abate-Shen et al., 2003], may play a major role in the development and progression of prostate cancer due to exposure to environmental carcinogens including those in cigarette smoke and the diet. To our knowledge, we have reported for the first time, the basal expression and B[*a*]P-induced expression of CYP1A1 and CYP1A2 in normal and primary tumor prostate cells 1542-NPTX and 1542-CP3TX, respectively. The CYP1A expression pattern for these cells differs from the metastatic cell lines DU145, PC3, and LNCaP. These prostate cells provide a model system for investigation of the molecular mechanisms for understanding prostate cancer development and progression from dietary and cigarette smoke aryl amines and PAHs.

Further significance of CYP1A expression levels in prostate cells is due to the likelihood of dietary and cigarette smoke precarcinogens and their CYP1A-mediated ultimate carcinogenic metabolites having the potential to target prostate specific tumor suppressor genes such as *Nkx3.1* that may be directly involved in prostate cancer development. Also, CYP1A precarcinogenic substrates can disrupt androgen receptor function. In addition, increased CYP1A activity can compromise the efficacy of anti-androgenic and other prostate cancer therapeutic drugs due to increased metabolism.

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REFERENCES

Abate-Shen C, Banach-Petrosky WA, Sun X, Economides KD, Desai N, Gregg JP, Borowsky AD, Cardiff RD, Shen MM. 2003. Nkx3.1; Pten mutant mice develop invasive prostate adenocarcinoma and lymph node metastases. Cancer Res 63:3886–3890.

Andersson SO, Baron J, Bergstrom R, Lindgren C, Wolk A, Adami HO. 1996. Lifestyle factors and prostate cancer risk: A case-control study in Sweden. Cancer Epidemiol Biomarkers Prev 5:509–513.

Battula N, Townsend GK, Snyderwine EG, Schut HA, Thorgeirsson SS. 1990. Preferential activation and genotoxicity of food derived heterocyclic amine mutagens by recombinant cytochrome P4501A2. Prog Clin Biol Res 347:55–69.

Bhatia-Gaur R, Donjacour AA, Sciavolino PJ, Kim M, Desai N, Young P, Norton CR, Gridley T, Cardiff RD, Cunha GR, Abate-Shen C, Shen MM. 1999. Roles for Nkx3.1 in prostate development and cancer. Genes Dev 13:966–977.

Boucher PD, Piechocki MP, Hines RN. 1995. Partial characterization of the human CYP1A1 negatively acting transcription factor and mutational analysis of its cognate DNA recognition sequence. Mol Cell Biol 15:5144–5151.

Bright RK, Vocke CD, Emmert-Buck MR, Duray PH, Solomon D, Fetsch P, Rhim JS, Linehan WM, Topalian SL. 1997. Generation and genetic characterization of immortal human prostate epithelial cell lines derived from primary cancer specimens. Cancer Res 57:995–1002.

Carter HB, Coffey DS. 1990. The prostate: An increasing medical problem. Prostate 16:39–48.

Catteau A, Douriez E, Beaune P, Poisson N, Bonaiti-Pellie C, Laurent P. 1995. Genetic polymorphism of induction of CYP1A1 (EROD) activity. Pharmacogenetics 5:110–119.

Conney AH. 1967. Pharmacological implications of microsomal enzyme induction. Pharmacol Rev 19:317–366.

Conney AH. 1982. Induction of microsomal enzymes by foreign chemicals and carcinogenesis by polycyclic

aromatic hydrocarbons: G.H.A. Clowes Memorial Lecture. Cancer Res 42:4875–4917.

Coughlin SS, Neaton JD, Sengupta A. 1996. Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial. Am J Epidemiol 143:1002–1006.

Fujino T, Gottlieb K, Manchester DK, Park SS, West D, Gurtoo HL, Tarone RE, Gelboin HV. 1984. Monoclonal antibody phenotyping of interindividual differences in cytochrome P-450-dependent reactions of single and twin human placenta. Cancer Res 44:3916–3923.

Haenzel W, Kurihara M. 1968. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 40:43–68.

Hayashi Y, Sugimura T. 1994. New thoughts on carcinogenic risk assessment of environmental chemicals. Exp Toxicol Pathol 46:51–54.

Hines RN, Mathis JM, Jacob CS. 1988. Identification of multiple regulatory elements on the human cytochrome *P450IA1* gene. Carcinogenesis 9:1599–1605.

Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HT, Blot WJ. 1990. Diet, tobacco use, and fatal prostate cancer: Results from the Lutheran Brotherhood Cohort Study. Cancer Res 50: 6836–6840.

Hsing AW, McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF, Jr. 1991. Tobacco use and prostate cancer: 26-Year follow-up of US veterans. Am J Epidemiol 133:437–441.

Ilett KF, Castleden WM, Vandongen YK, Stacey MC, Butler MA, Kadlubar FF. 1993. Acetylation phenotype and cytochrome P450IA2 phenotype are unlikely to be associated with peripheral arterial disease. Clin Pharmacol Ther 54:317–322.

Jana NR, Sarkar S, Ishizuka M, Yonemoto J, Tohyama C, Sone H. 1999. Cross-talk between 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and testosterone signal transduction pathways in LNCaP prostate cancer cells. Biochem Biophys Res Comm 256:462–468.

Kadlubar FF, Butler MA, Kaderlik KR, Chou HC, Lang NP. 1992. Polymorphisms for aromatic amine metabolism in humans: Relevance for human carcinogenesis. Environ Health Perspect 98:69–74.

Kalow W, Tang BK. 1991. Use of caffeine metabolite ratios to explore CYP1A2 and xanthine oxidase activities. Clin Pharmacol Ther 50:508–519.

Kizu R, Okamura K, Toriba A, Kakishima H, Mizokami A, Burnstein KL, Hayakawa K. 2003. A role of aryl hydrocarbon receptor in the antiandrogenic effects of polycyclic aromatic hydrocarbons in LNCaP human prostate carcinoma cells. Arch Toxicol 77:335–343.

Kouri RE, Nebert DW. 1977. Origins of Human Cancer. In: Hiatt HH, Watson JD, Winsten JA, editors. NY: Cold Spring Harbor Laboratory; pp 811–835.

Kouri RE, McKinney CE, Slomiany DJ, Snodgrass DR, Wray NP, McLemore TL. 1982. Positive correlation between high aryl hydrocarbon hydroxylase activity and primary lung cancer as analyzed in cryopreserved lymphocytes. Cancer Res 42:5030–5037.

Laemmli UK. 1970. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature 227:680–685.

McManus ME, Burgess WM, Veronese ME, Huggett A, Quattrochi LC, Tukey RH. 1990. Metabolism of 2-acetylaminofluorene and benzo(a)pyrene and activation of food-derived heterocyclic amine mutagens by human cytochromes P-450. Cancer Res 50:3367–3376.

Morville AL, Thomas P, Levin W, Reik L, Ryan DE, Raphael C, Adesnik M. 1983. The accumulation of distinct mRNAs for the immunochemically related cytochromes P-450c and P-450d in rat liver following 3-methylcholanthrene treatment. J Biol Chem 258:3901–3906.

Murray GI, Foster CO, Barnes TS, Weaver RJ, Ewen SW, Melvin WT, Burke MD. 1991. Expression of cytochrome P450IA in breast cancer. Br J Cancer 63:1021–1023.

Murray BP, Edwards RJ, Murray S, Singleton AM, Davies DS, Boobis AR. 1993. Human hepatic CYP1A1 and CYP1A2 content, determined with specific anti-peptide antibodies, correlates with the mutagenic activation of PhIP. Carcinogenesis 14:585–592.

Murray GI, Taylor VE, McKay JA, Weaver RJ, Ewen SW, Melvin WT, Burke MD. 1995. The immunohistochemical localization of drug-metabolizing enzymes in prostate cancer. J Pathol 177:147–152.

Nakajima M, Yokoi T, Mizutani M, Shin S, Kadlubar FF, Kamataki T. 1994. Phenotyping of CYP1A2 in Japanese population by analysis of caffeine urinary metabolites: Absence of mutation prescribing the phenotype in the *CYP1A2* gene. Cancer Epidemiol Biomarkers Prev 3: 413–421.

Nebert DW, Gonzalez FJ. 1987. *P450* genes and evolutionary genetics. Hosp Pract (Off Ed) 15:63–74.

Pelkonen O, Nebert DW. 1982. Metabolism of polycyclic aromatic hydrocarbons: Etiologic role in carcinogenesis. Pharmacol Rev 34:189–222.

Pyykko K, Tuimala R, Aalto L, Perkio T. 1991. Is aryl hydrocarbon hydroxylase activity a new prognostic indicator for breast cancer? Br J Cancer 63:596–600.

Relling MV, Lin JS, Ayers GD, Evans WE. 1992. Racial and gender differences in *N*-acetyltransferase, xanthine oxidase, and CYP1A2 activities. Clin Pharmacol Ther 52:643–658.

Ries LAG, Miller BA, Hankey BF, et al., editors. 1994. SEER cancer statistics review, 1973–1991; tables and graphs. Bethesda, MD: National Cancer Institute, (NIH publication no. 94-2789).

Rodriguez C, Tatham LM, Thun MJ, Calle EE, Heath CW, Jr. 1997. Smoking and fatal prostate cancer in a large cohort of adult men. Am J Epidemiol 145:466–475.

Schaufler K, Haslmayer P, Jager W, Pec M, Thalhammer T. 2002. The environmental toxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin induces cytochrome P450 activity in high passage PC 3 and DU 145 human prostate cancer cell lines. Int J Mol Med 9:411–416.

Schweikl H, Taylor JA, Kitareewan S, Linko P, Nagorney D, Goldstein JA. 1993. Expression of *CYP1A1* and *CYP1A2* genes in human liver. Pharmacogenetics 3:239–249.

Sesardic D, Pasanen M, Pelkonen O, Boobis AR. 1990. Differential expression and regulation of members of the cytochrome *P450IA* gene subfamily in human tissues. Carcinogenesis 11:1183–1188.

Sherson D, Sigsgaard T, Overgaard E, Loft S, Poulsen HE, Jongeneelen FJ. 1992. Interaction of smoking, uptake of polycyclic aromatic hydrocarbons, and cytochrome P450IA2 activity among foundry workers. Br J Ind Med 49:197–202.

Sterling K, Bresnick E. 1996. Oct-1 transcription factor is a negative regulator of rat CYP1A1 expression via an octamer sequence in its negative regulatory element. Mol Pharmacol 49:329–337.

Sutter TR, Guzman K, Dold KM, Greenlee WF. 1991. Targets for dioxin: Genes for plasminogen activator inhibitor-2 and interleukin-1 beta. Science 254:415–418.

Thomas PE, Reik LM, Ryan DE, Levin W. 1983. Induction of two immunochemically related rat liver cytochrome P-450 isozymes, cytochromes P-450c and P-450d, by structurally diverse xenobiotics. J Biol Chem 258:4590–4598.

Tilley WD, Wilson CM, Marcelli M, McPhaul MJ. 1990. Androgen receptor gene expression in human prostate carcinoma cell lines. Cancer Res 50:5382–5386.

Vistisen K, Poulsen HE, Loft S. 1992. Foreign compound metabolism capacity in man measured from metabolites of dietary caffeine. Carcinogenesis 13:1561–1568.

Whitlock JP, Jr. 1986. The regulation of cytochrome *P-450* gene expression. Annu Rev Pharmacol Toxicol 26:333–369.

Whitlock JP, Jr. 1999. Induction of cytochrome P4501A1. Ann Rev Pharmacol Toxicol 39:103–125.

Williams JA, Martin FL, Muir GH, Hewer A, Grover PL, Phillips DH. 2000. Metabolic activation of carcinogens and expression of various cytochromes P450 in human prostate tissue. Carcinogenesis 21:1683–1689.

Wingo PA, Tong T, Bolden S. 1995. Cancer statistics, 1995. CA Cancer J Clin 45:8–30.

Wrighton SA, Campanile C, Thomas PE, Maines SL, Watkins PB, Parker G, Mendez-Picon G, Haniu M, Shively JE, Levin W, et al. 1986. Identification of a human liver cytochrome P-450 homologous to the major isosafrole-inducible cytochrome P-450 in the rat. Mol Pharmacol 29:405–410.