# Chapter 2
# Gene–Environment Interactions, Phenotypic Changes, and Human Health

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**Abstract** The contribution of the environment to the development of chronic disease has historically been documented. As early as 1775, scrotal and nasal cancer was observed among chimney sweepers in London, England by British physician, Percival Potts. His hypothesis was that these cancers were induced by cumulative environmental exposure to chimney soot as they worked. The discipline of cancer epidemiology has continued in the tradition of Dr. Potts. The purpose of this discipline has not been to prove a cause-effect relationship between exposure and development of disease but to identify the "common thread" of exposures. Today, cancer epidemiology incorporates various scientific disciplines (i.e., risk assessment, toxicology, cellular and molecular biology) to quantify the dose-response relationship between an individual and suspect environmental factor. With the completion of the Human Genome Project in 2003, we now know that individual genetic variability plays a significant role in modifying the effect of environmental exposures on disease development. Additionally, the utility of assessing the individual's genetic variability is invaluable in estimating the degree of severity at time of diagnosis as well as the risk of metastasis and other complications. This chapter explores the relationship of gene–environment interactions in cancer from an environmental epidemiology and public health perspective.

**Keywords** Gene–environment interactions · Cancer · Environmental epidemiology · Public health perspective

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## 2.1 History of the Relationship Between Genes, Environment, and Human Disease

The belief that the environment plays a critical role in human disease development dates back to the 1700s. As early as 1775, Dr. Percival Potts reported that the incidence of scrotal cancer among chimney sweeps was linked to their occupational exposure to soot (Harrison, 2004). In 1854, Dr. John Snow documented that a cholera outbreak in the Soho area of London, England could be traced to a specific public water source; the Broad Street Pump (Newsom, 2006). Through the use of statistics and geographical maps (i.e., geographic epidemiology) showing the neighborhood-specific distribution of disease incidence, he was able to convince public officials to remove this environmental hazard and eventually the incidence of cholera diminished. In more modern times, environmental exposures that are associated with human disease include poor air quality, hazardous chemicals in the occupational setting, agricultural pesticides, and personal lifestyle choices (i.e., smoking, alcohol use, diet). However, it has become apparent that not every individual who is exposed to a particular environmental factor (i.e., cigarettes, heavy drinking, a high-fat diet) will develop the associated disease (i.e., lung, liver, or pancreatic cancer, respectively). Furthermore, diseases with an environmentally-related etiology are no longer restricted to cancer and now include asthma, cardiovascular disease, and obesity (Bernal-Pacheco and Roman, 2007; Grarup and Andersen, 2007, Newbold et al., 2007; Rundle et al., 2007; Heinrich et al., 2008).

The variability of an individual's response to environmental stimuli was originally thought to have been a function of the dose of the environmental stimuli and the route of exposure. More recently, these risk assessments have expanded the definition of "environmental stimuli" to include social and economic risk factors (i.e., educational attainment, housing characteristics). In addition to disease development being the "response", researchers now examine the incidence of health complications and reduction in quality of life. With the evolution of genomics, individual variability in response to environmental stimuli is better understood. The completion of the Human Genome Project has resulted in considering one's genotype as an additional risk factor in dose-response risk assessments. Additionally, the Human Genome Project has given rise to two emerging and exciting fields; molecular epidemiology and bioinformatics.

Molecular epidemiology is a multi-disciplinary field that seeks to characterize the prevalence of functional biomarkers among diseased and non-diseased populations (Khoury et al., 2004, 2005). With the emergence of this discipline, the ability to quantify the relationship between environmental exposures and disease-specific mechanisms is now possible. Thus, molecular epidemiology allows a novel approach to improve population health by identifying the patterns of variability that increase the risk for disease morbidity and mortality. Bioinformatics is a field that was developed in response to the need of molecular biologists who required the creation and management of large datasets containing nucleotide and amino sequences as well as protein domains and structures that could be queried and one

where updates could be routinely performed (National Center for Biotechnology Information, 2004). Thus, the field of bioinformatics was well-suited to assume the task of merging the information from molecular biology and epidemiology studies. Ultimately, the powerful analytical tools of molecular epidemiology and bioinformatics will enable biomedical researchers to assess the contribution from multiple sources of risk (i.e., genes, social/physical environment) towards normal and "not-so-normal" physiological processes.

## 2.2 Health Disparities and Genetics

Historically, disproportionate rates of disease and mortality have been attributed to the lack of adequate economic and social "safety nets". The aforementioned Broad Street Pump event in 1850s London, England was highly influenced by the concentration of inadequate housing and the poor in the Pump's immediate vicinity (Newsom, 2006). When the pump was closed, the cholera epidemic virtually disappeared. Other significant advances in controlling the spread of infectious disease were possible due to the development of vaccines during the twentieth century. Although the overall vaccination rates for the US population are approximately 90%, lower rates among subgroups (i.e., minorities, poor, elderly) continue to persist due to barriers to health care and lack of health information (Szilagyi et al., 2002). Community-based strategies that target these barriers and improve vaccination rates have become working models for vaccine programs, especially within the medically underserved areas in the US. More recently, preventive care (i.e., screening for cancer, hypertension, diabetes) has emerged as a leading public health issue. Studies examining the effect of promoting preventive care have shown that mortality rates due to cardiovascular disease and colon, prostate, and breast cancer have steadily decreased for most groups since the 1990s. However, these studies have also shown that females, the poor, and ethnic/racial minorities still experience higher rates of morbidity due to preventable chronic diseases (Lander et al., 2001; CDC National Office of Public Health Genomics, 2004; Chien et al., 2005; Chlebowski et al., 2005; Doty and Holmgren, 2005, Commonwealth Fund, 2006; Harris et al., 2006; Blendon et al., 2007; Graham et al., 2007). These studies suggest that underlying societal, institutional, and economic factors continue to influence the persistence of health disparities even with increased public health strategies. Thus, it has become obvious that the issue of health disparities in the US is complex and multi-factorial for which there is no "magic bullet" solution.

The role of individual genetic variability in response to common environmental stimuli has long been suspected as being a significant contributor to the prevalence of health disparities. Many in the biomedical research community had envisioned that the Human Genome Project would finally provide the tools to quantify the genetic contribution to health disparities. It was soon apparent that genetics explained only a fraction of disparities in chronic disease. However, the

Human Genome Project has helped biomedical researchers identify trends in functional genomic variability (i.e., gene–protein interactions) among populations who experience greater disease morbidity and mortality (i.e., the disease phenotype). Often the inciting event for these disparate trends is the environmental exposure to one or more agents. An example of such is the exposure to cigarette smoking and asbestos. Individually, asbestos exposure and cigarette smoking confer a degree of risk for cancer development. However, together these environmental agents act synergistically to influence the resulting cancer phenotype (i.e., stage of invasiveness at diagnosis) (Liddell, 2001; Berry and Liddell, 2004). Additionally, if these exposures occur in an individual who is genetically predisposed to reduced bioavailability to detoxifying enzymes, such as cytochrome P-450 or glutathione-S-transferase, the risk for cancer is significantly higher (Christiani, 2000).

An emerging interest of molecular epidemiologists is the characterization of common, functional haplotypes among diseased individuals. Haplotypes are defined as a set of single nucleotide polymorphisms (SNPs) on a chromatid whose association is statistically significant (National Human Genome Research Institute, 2007). Thus, the identification of functional haplotypes among those who are experiencing greater morbidity due to a chronic disease would be invaluable. Furthermore, haplotype studies of various SNPs that demonstrate significant association with disease would provide further insight to explain disparities of disease severity.

## 2.3 Studying Gene–Environment Interactions and Disease

The current environment of risk-exposure assessments is one of great opportunity. Improving population health using newer and more powerful predictive models to quantify the cumulative contribution from multiple sources of risk (i.e., exposure, age, gender, genes) continue to be developed. The movement of modern biomedical research to a collaborative, multidisciplinary effort exemplifies the complexity of the genomic contribution to human health and disease. Table 2.1 lists some of the largest initiatives that will likely have an impact on global health in the near future.

The National Institutes of Health (NIH) recently launched the Genetic Association Information Network (GAIN) which is a public-private partnership that will fund studies which aim to examine genome-wide associations in diseases such as depression, and certain autoimmune disorders (National Human Genome Research Institute, 2006). The Genes, Environment, and Health (GEI) Initiative is another NIH program that seeks to further our understanding of gene–environment interactions by identifying new pathways of interaction and developing newer measurements of an individual's response to environmental stimuli including genomics, proteomics, and metabolomics (National Institutes of Health, 2007). Building on their prior successes with the Framingham Heart Study, the National Heart, Lung, and Blood Institute (NHLBI) of the NIH has retained 9,000 of the original Framingham Study participants and their family members for the Framingham

**Table 2.1** Summary of the largest gene by environment initiatives that will affect global public health

| | Objective(s) | Citations |
|---|---|---|
| The NIH Long Life Family Study http://www.longlifefamilystudy.org/ | 1. Identify characteristics of exceptional families that protect them from disease and disability, including lifestyle and genes<br>2. Identify positive factors that influence their longevity is also of interest | 1. *In the genes: Searching for Methuselah.* NIH Medline Plus Winter 2007<br>2. *Live long? Die young? Answer isn't just in genes*. New York Times, Aug. 31, 2006 |
| The NIH Road Map Initiative http://nihroadmap.nih.gov/ | 1. To identify major opportunities and gaps in biomedical research<br>2. Lays out a vision for a more efficient and productive system of medical research<br>3. Identifies the most compelling opportunities in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise | *The NIH roadmap*. Science, Vol. 302, 3 Oct. 2003 |
| National Center for Toxicogenomics | To determine how disease may be influenced by environmental factors using bioinformatics combined with microarray-based strategies | *National Center for Toxicogenomics: An intoduction.* Environmental Health Perspectives Vol. 111, No. 1T, Jan. 2003 |
| Chemical Effects in Biological Systems Knowledgebase (CEBS) http://cebs.niehs.nih.gov/cebs | Integrates study design, clinical pathology, and histopathology data from all studies to enable discrimination of critical study factors | *Systems toxicology and the chemical effects in biological systems (CEBS) knowledge Base.* Environmental Health Perspectives Toxicogenomics, Vol. 111, IT, Jan. 2003 |
| The SNP Consortium http://snp.cshl.org | Identified and mapped 1.5 million individual single nucleotide polymorphisms (SNPs) which are genetic markers (sequence "landmarks" in the genome) used to create genetic maps. These data have been made publicly available to researchers over the internet | *The SNP consortium* website: past, present and future. Nucleic Acids Research, Vol. 31, No. 1, pp. 124–127, 2003 |

**Table 2.1** (continued)

| | Objective(s) | Citations |
|---|---|---|
| HapMap Project http://www.hapmap.org/ | Aims to map the patterns of common SNP variation across the globe and to examine at combinations of SNPs that are inherited together, known as haplotypes | *A second generation human haplotype map of over 3.1 million SNPs.* Nature, Vol. 449, pp. 851–861, 2007 |
| International Cancer Genome Consortium | The project aims to avoid duplication and waste by coordinating the cancer types studied and by establishing common standards of data collection and analysis | *International consortium to tackle cancer genomes.* Published online 30 April 2008, Nature, doi:10.1038/453015a |
| NIH Cancer Genome Atlas Project | Co-funded by the National Cancer Institute and the National Human Genome Research Institute, this project seeks to the prevention, diagnosis, and treatment of cancer through genome surveillance—monitoring the genome for subtle changes that are suspected of contributing to cancer morbidity and mortality | *NIH Institutes launch joint venture to map cancer genome.* Journal of the National Cancer Institute, Vol. 98, No. 3, February 1, 2006 |
| The NIEHS Sister Study | A landmark study that seeks to untangle the link between the environment and breast cancer. This study envisions the enrollment of 50,000 female volunteers who have has a sister diagnosed with breast cancer | *Sister study hopes to answer breast cancer questions*. Environmental Health Perspectives, Vol. 109, No. 8, August 2001 |

Genetic Research Study. This study aims to identify genes that may underlie diseases, such as heart disease and stroke, across three generations of family members (National Heart Lung and Blood Institute, 2006). Using the aforementioned model, genome-wide association studies are being planned using pooled DNA samples obtained from the cohorts of the NIH's Women's Health Study and the Women's Health Initiative.

Twin studies have provided great insight to the familial or inherited contribution to disease development. In Finland, a landmark study of like- and opposite-sexed monozygotic (MZ) and dizygotic (DZ) twins has continued to examine the concordance and discordance of genetic traits with respect to cancer, obesity, osteoarthritis, asthma, and cardiovascular disease (Verkasalo et al., 1999; Lichtenstein et al., 2000). However, an exclusive genetic contribution to disease development in the study group ($n > 3{,}000$) has been less than 20%. Other twin studies have provided the evidence supporting the contribution of environmental factors, including the social and parental environment, to disease development among MZ and DZ twins such as depression and addiction disorders. More recently, it has been suggested that differential environmental exposures induce epigenetic changes in cells and this could be the mechanism that explains discordance for disease development among MZ twins (Poulsen et al., 2007).

The contribution of race or ethnicity towards the development of environmentally-related disease has been studied extensively amongst Ashkenazi Jews (i.e., of medieval German origin). Such studies have found a disproportionately higher incidence of breast and ovarian cancer among this population when compared to other populations. One explanation for this trend is provided by a recent study that found a higher prevalence (8%) of abnormal breast cancer (BRCA 1) genes among Ashkenazi Jew females diagnosed with breast cancer (John et al., 2007). In the same study, the authors found a lower prevalence (2%) of this risk factor for breast and ovarian cancer among white Anglo females. However, most cancer studies that have sought a race-ethnic basis for cancer disparities have had contradictory results. Most of the contradiction is due to differential environmental exposures which are now recognized as powerful confounding factors.

## 2.4 The Environment, Genes, and Cancer

The contribution of the environment to the incidence of cancer is not a new hypothesis. In fact, decades of epidemiological studies have revealed that risk conferred environmental factors is significant for 80–90% of newly-diagnosed cancers. However, many of these studies state that environmental exposures alone are not sufficient to incite the development of cancer. This suggests that an individual's genotype confers some degree of susceptibility to the ill-effects of environmental exposures such as tobacco smoke, alcohol use and exposure to industrial and agricultural chemicals. Additionally, the definition of environmental risk factors for cancer has expanded to include one's diet, the "built environment" and physical

activity. This section will discuss the current evidence for a gene–environment interaction in the risk for diagnosis of cancer as well as the increased risk of death due to cancer. To ease the reading of the following section, a glossary of frequently used terms is provided in Table 2.2 and a list of candidate genes, including their abbreviations, and their functions, is provided in Table 2.3. A summary of the evidence presented in this section supporting the relationship between genes, environmental exposures and cancer is found in Table 2.4.

### *2.4.1 Bladder Cancer*

The National Cancer Institute (NCI) estimated that for the year 2008, there were 68,810 new cases of bladder cancer and an additional 14,100 lives lost (National Cancer Institute, 2007a). Gender disparities have been observed in the risk for bladder cancer among male smokers (OR = 7.1) when compared to female smokers (OR = 5.1). However, this disparity is reversed among non-smokers as the effect cumulative exposure to environmental tobacco smoke on bladder cancer incidence appears to affect more women than men (Anton-Culver et al., 1993). Studies have shown that although the frequency of bladder cancer diagnosis is 50% higher in Whites, the mortality rate among Whites and African-Americans is comparable (Prout et al., 2000). This suggests that bladder cancer in African-Americans is either diagnosed at a later stage of disease or this group is more susceptible to an aggressive form of this disease.

The altered expression of carcinogen detoxifying genes (i.e., NAT2, GSTM1) and the DNA repair enzymes (i.e., NER enzymes) have been shown to confer an increased risk of bladder cancer. A 2006 study of the role NER genes plays in bladder cancer found that possessing one of the 22 SNPs that are found in seven NER genes significantly predicted the incidence of bladder cancer risk ($p = 0.04$) (Garcia-Closas et al., 2006). Further pair-wise association analysis found that the risk of bladder cancer increased 1.5–2-fold when the variants were carried in both copies of four of the seven genes being studied.

The risk of bladder cancer from the decreased production of enzymes responsible for detoxification or DNA repair is further increased among cigarette smokers. A gene–environment interaction is biologically plausible since NAT2 and GSTM1 are responsible for detoxifying the cigarette-containing compounds, aromatic amines and polycyclic aromatic hydrocarbons. These compounds are also known to induce DNA damage. In 2005, a meta-analysis conducted by Garcia-Closas et al. found an increased risk of bladder cancer among smokers with SNPs in either NAT2 gene ($p = 0.008$) or the GSTM1 gene ($p < 0.0001$) (García-Closas et al., 2005). An examination by this same group of investigators found that the risk for bladder cancer among individuals with a SNP in one of the NER enzyme genes conferred a significant risk ($p = 0.02$) but SNPs in two genes conferred a much more substantial risk ($p < 0.001$) (Garcia-Closas et al., 2006).

The distribution of the NAT2 and GSTM1 alleles has been estimated to be 40 and 50%, respectively, in the European and the US White populations (Vineis, 2004).

**Table 2.2** Glossary of terms used in this chapter

| | |
|---|---|
| Genotype | The genetic constitution of an individual |
| Phenotype | The observable properties of an organism that are produced by the interaction of the genotype and the environment |
| Bioavailability | The degree and rate at which a substance, such as an endogenous protein, is made available at the site of physiological activity |
| Healthy people | A set of health objectives for the Nation to achieve over the prescribed decade. Healthy People 2010 outlined the objectives for the decade 2000–2010; Healthy People 2020 will outline the objectives for the decade 2010–2020. It can be used by many different people, States, communities, professional organizations, and others to help them develop programs to improve health |
| Single nucleotide polymorphisms (SNPs) | Sites in the DNA sequence where individuals differ at a single DNA base |
| Haplotype | Defined as a set of proximal single nucleotide polymorphisms (SNPs) on a chromatid that are inherited together in a "block" and whose association is statistically significant. The block of SNPs that characterize the haplotype are referred to as "tag SNPs" |
| Framingham heart study | The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to cardiovascular disease by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. To date, the study has expanded to three generations of related participants |
| Women's Health Initiative (WHI) | is a long-term national health study that focuses on strategies for preventing heart disease, breast and colorectal cancer and fracture in postmenopausal women. This 15-year project involves over 161,000 women ages 50–79, and is one of the most definitive, far reaching programs of research on women's health ever undertaken in the US |
| Odds ratio (OR) | The unit of measure used to compare the presence of a risk factor for disease in a sample of diseased subjects vs. non diseased controls. An odds ratio = 1 indicates no risk; an odds ratio < 1 = a protective factor; an odds ratio > 1 = a risk factor. Additionally, the odds ratio is accompanied by a 95% confidence interval (i.e. that there is < a 5% likelihood that the risk is attributed to chance). When the confidence interval includes 1, the odds ration is considered "not statistically significant" |
| Oncogene | A gene that normally directs cell growth. When mutated, an oncogene can promote and/or allow the uncontrolled growth of cancer. Mutations to oncogenes occur via environmental exposures or hereditary factors |
| Tumor suppressor gene (also known as anti-oncogene) | Responsible for producing the protein that controls cell growth. When mutated, aberrant cell growth and subsequently cancer, may occur. As with oncogene, mutations to tumor suppressor genes can occur via environmental exposures or hereditary factors |

**Table 2.3** Dictionary of genes cited in this chapter

| Gene | Abbreviation | Category | Function |
|---|---|---|---|
| Alcohol dehydrogenase | ADH | Detoxification of ethanol | ADH is a group of enzymes that function to metabolize ingested alcohols which could otherwise be toxic. The production of this enzyme is lower in females when compared to males and its genetic expression is higher among those of European ancestry when compared to those of Asian ancestry |
| Aldehyde dehydrogenase | ALDH | Detoxification of ethanol | ALDH is a group of enzymes that function to metabolize aldehydes, the intermediate products of alcohol degradation |
| Ataxia-telangiectasia | ATM | DNA repair | ATM controls cell growth by coordinating DNA repair via activation of other proteins |
| Breast cancer Type 1 or Type 2 susceptibility gene | BRCA1<br>BRCA2 | Tumor suppressor gene | BRCA genes participate in repairing cells with breaks in double-stranded DNA |
| Cell-cycle checkpoint kinase | CHEK2 | Cell cycle regulation | CHEK2 is an enzyme is critical for cell cycle regulation via apoptosis and DNA repair via cell cycle arrest |
| Cytochrome p450 | CYP1A1<br>CYP1B1<br>CYP2E1 | Phase 1 detoxification | CYP450 enzymes are primarily tasked with the Phase 1 detoxification and biotransformation of xenobiotics. Specifically, CYP450 is a family of heme proteins tasked with the breakdown of exogenous substances (i.e., drugs and toxic compounds) as well as endogenous metabolic products (i.e., bilirubin, the breakdown product of hemoglobin) |
| Epoxide hydrolase | EPHX | Phase 2 detoxification | An enzyme that functions in detoxification during drug metabolism. This enzyme is critical in the conversion of intermediate metabolites (epoxides) to compounds that can be excreted from the body. These metabolites, which are generated as a result of cytochrome P450 break-down of aromatic compounds, are also mutagenic |
| Glypican 3 | GPC3 | Organ and tissue development | GPC 3 is an oncofetal protein. An oncofetal protein is one that is expressed during embryogenesis and is involved in organogenesis. The exact biological function of GPC3 is not known. However, GPC3 has been observed to be over-expressed in liver and skin cancer tumors |

**Table 2.3** (continued)

| Gene | Abbreviation | Category | Function |
|---|---|---|---|
| Glutathione-S-transferase M, T, P variants | GSTM1<br>GSTT1<br>GSTP1 | Phase 2 detoxification | GST enzymes play a critical role in the detoxification of various intermediate metabolites. These metabolites are often reactive inducing DNA damage and damage to DNA repair processes thus increasing the risk of carcinogenesis |
| Human epidermal growth factor receptor 2 | HER2/neu | Growth factor | HER2 is known to regulates cell growth and differentiation. The expression of HER2 on tumors is a critical for chemotherapy. Tumors that are negative for HER2 have poor response to chemotherapy |
| Midkine | MDK | Growth factor | Several cancers report an over-expression of MDK and is a pre-operative predictor of prognosis, including metastases. However, the exact mechanism by which it influences cancer prognosis is not known |
| Myeloperoxidase | MPO | Phase 1 detoxification | MPO plays a role in the metabolic activation of pro-carcinogens found in cigarettes. Thus, differential expression of this enzyme has been hypothesized to influence the risk of lung cancer among smokers |
| Methylenetetrahydrofolate reductase | MTHFR | Conversion of ingested folic acid to bioactive form | MTHFR catalyzes the bioconversion of folic acid or vitamin B9. This is significant since dietary sources of methyl donors (i.e., folic acid) are hypothesized to decrease the risk of cancers of the digestive system |
| N-acetyl transferase | NAT2 | Phase 2 detoxification | This family of enzymes facilitates the biotransformation of intermediate metabolites from Phase 1 detoxification via acetylation. These metabolites include polycyclic hydrocarbons that are found in cigarettes and cigarette smoke |
| Nucleotide excision repair | NER | DNA repair | NER enzymes are critical for DNA repair in damaged cells, specifically that which occurs as a result of oxidative damage |

**Table 2.3** (continued)

| Gene | Abbreviation | Category | Function |
|---|---|---|---|
| NAD(P)H:quinone acceptor xidoreductase | NQO | Phase 2 detoxification | NQO enzymes are a family of enzymes that detoxify endogenous and exogenous substances via reduction of the intermediate metabolite, quinones, via electron reduction reactions. This enzymatic activity protects cells against oxidative stress; a risk factor for carcinogenesis |
| Tumor protein 53 | TP53 | Cell cycle regulation | This gene regulates the cell cycle via cell cycle arrest when damage to DNA occurs and if necessary, induction of apoptosis. Because of this function, it is often referred to as the guardian of the genome especially since it is a key player in the anti-cancer activities of many cells |
| Progression elevated gene | PEG10 | Tumor progression | The expression of this gene is elevated in the presence of DNA damage and during cancer cell progression. Its expression also correlates with genomic stability |
| Phosphatase and tensin homolog deleted on chromosometen | PTEN | Tumor suppressor gene | Cell cycle regulation via signaling to damaged cells to stop dividing and undergo apoptosis |
| Thymidylate synthase | TS | | |
| Excision repair cross-complementing group 2 | XDP (also known as ERCC2) | DNA repair | Transcription-coupled nucleotide excision repair |
| X-ray repair cross-complementing group | XRCC | DNA repair | Base excision repair |
| V-raf murine sarcoma viral oncogene homolog B1 | BRAF | Oncogene | A mutated form of the normal, cellular genes, known as proto-oncogenes, that contributes to the production of a cancer. Since they direct cell growth, the mutated oncogenes are hypothesized to increase the growth and spread of cancer cells |

**Table 2.3** (continued)

| Gene | Abbreviation | Category | Function |
|---|---|---|---|
| Melanocortin-1-recpetor | MC1R | Production of melanin | A key protein that regulates skin and hair color. It is found at the surface of cells that produce melanin called melanocytes. In the 1990s variants of the MC1R gene were found in 80% of humans who have red hair and fair skin. Individuals with skin cancer also have a higher frequency of mutations in this gene although the exact mechanism responsible remains unknown |
| 8q24 | | Region (locus) on chromosome 8 | Polymorphisms in the region of this locus on chromosome 8 have been shown to be significantly associated with prostate and breast cancer |
| Insulin growth factor | IGF1 | Cell cycle regulation | Through binding on various cells in various tissues, IGF stimulates cell growth and plays a critical role in anti-apoptotic activity |
| Estrogen receptor beta | ESR2 | Nuclear receptor | This protein plays a key role in DNA binding and subsequent gene transcription. It is normally expressed in the nucleus of normal epithelial and blood cells as well as their malignant counterparts |
| Androgen receptor | AR | Nuclear receptor | This protein plays a key role in DNA binding and subsequent gene transcription. Genes that are regulated by the androgen receptor are critical for the development and maintenance of the male sexual phenotype |
| Serine peptidase inhibitor, Kazal type 1 | SPINK1 | Trypsin inhibitor | Mutations of this protein are found to correlate with risk for acute and chronic pancreatitis |

**Table 2.4** Summary of the risk for cancer posed gene by environment interactions cited in this chapter

| Cancer | Candidate gene(s) | Environmental exposure(s) | Phenotypic change due to interaction between genes and environment |
|---|---|---|---|
| Bladder | NAT2<br>GSTM1<br>NER | Smoking confers higher risk in males | Substantial increase in risk for smokers with SNPs in these genes |
| | | Exposure to environmental tobacco smoke (ETS) confers higher risk for females | Effect of ETS on those with SNPs not known |
| Breast | CYP1B1 | Smoking | 2.6–5.1× increase in risk for breast cancer among smokers |
| | NAT2 | | 2.5× increase in risk among smokers |
| Colorectal | CYP2E1 | Frequent red meat or processed meat consumption | 2×–3× increase in risk for rectal cancer among heavy meat eaters |
| | XRCC | Smoking | 2.5× risk among "ever-smokers" |
| | XDP | Alcohol consumption | 2.9× risk among "ever-drinkers" |
| Esophageal | ADH | Alcohol consumption | 2× increase in risk amongst regular drinkers |
| | ALDH | | 2× risk among moderate drinkers<br>4.5× risk among heavy drinkers |
| Leukemia | CYP1A1 | Chemicals | CYP1A1 variants carriers: *In-utero* exposure to pesticides confers 5x increases risk of ALL; same exposure in childhood confers 3.6× increase in risk |
| | MTHFR<br>TS | Diet | Increased bioavailability of folate reduces risk for cancer |
| | CYP450<br>GST | | Gene–gene interactions among Phase I and Phase II enzyme genes (i.e., CYP450 and GST, respectively) with SNPs confer 2–10× risk for ALL |

**Table 2.4** (continued)

| Cancer | Candidate gene(s) | Environmental exposure(s) | Phenotypic change due to interaction between genes and environment |
|---|---|---|---|
| Liver | NAT2 | Smoking<br>Alcohol-related cirrhosis | The risk for liver cancer increases 2× for smokers with liver disease (from OR = 1.23 to OR =2.67) |
| | GSTM1 | Hepatitis infection | Risk from null GSTM1 genotype doubles from OR = 1.18 to OR = 1.26 in HepA infected patients |
| | EPHX | Heavy peanut butter consumption | Risk from heterozygous EPHX genotype increases from OR = 2.75 to OR = 3.63 among those with heavy peanut butter consumption |
| Lung | CYP1A1 | Smoking | 2× risk among light smokers (< 30 pack years) |
| | EPHX | Western lifestyle | 7× risk among young Mexican Americans |
| | GSTM1 and GSTP1 | Environmental tobacco smoke<br>Smoking | 2× risk among those with GSTM1 null genotype<br>4.5× risk among those with both GSTM1 null genotype and mutation in one or both GSTP1 alleles |
| | MPO | | 0.25 reduction in risk for lung cancer |
| | NAT2 | | 1.9× risk among smokers and non-smokers |
| Melanoma | BRAF2 and BRAF 4 | Male gender | Exact risk still not known |
| Mesothelioma | GSTM1 | Asbestos-occupational exposure | 1.9× risk among carriers of NAT2 fast-acetylator genotype |
| | NAT2 | | 2.4× risk among carriers of *BOTH* NAT2 fast acetylator and GSTM1-null genotypes |
| Pancreatic | NQO1 | Smoking | NQO1 levels were 6× greater |
| | GSTT1 | | GSTT-null genotype conferred a 5.0× increased risk among White female “ever” smokers and 3.2× risk among White male “ever” smokers |
| Prostate | GSTM | Smoking | 3.8× increased risk among smokers ( > 30 pack years) |
| | GSTP | Diet rich in cruciferous vegetables | Protective relationship has been established in-vitro |
| | NAT2 | Smoking | 2× risk among smokers |

However, the global distribution of the NER genes is harder to quantify since they are numerous and have overlapping functions. Genome screening projects, such as the HapMap project, continue to identify the NER gene variants that confer the most risk individually or in tandem with SNPs of other detoxifying or DNA repair genes. The knowledge generated from studies, such as the HapMap project, will have a substantial impact on how human health risk assessments are conducted in the future.

### *2.4.2 Breast Cancer*

Breast cancer has long been a threat to women's health. In 2008, the NCI estimated that 182,460 women were be diagnosed with breast cancer and claimed the lives of 40,480 (National Cancer Institute, 2007b). In spite of this grim statistic, it is encouraging that both breast cancer incidence and mortality have shown a downward trend over the past 20 years. This is likely a result of improved public health outreach and communication strategies that seek to increase awareness of screening and knowledge of risk factors among women and their health care providers.

As with other chronic diseases, higher rates of breast cancer mortality are observed for African-American females when compared to the national average (i.e., 33.5/100,000 and 25.0/100,000, respectively). Even more disturbing is the fact that this disparity exists even as the diagnostic rate of breast cancer is lower among African-American females (i.e., 117.5/100,000) when compared to national rate (i.e., 126.1/100,000) (Ries et al., 2008). Studies have shown that African-American women are less likely to be screened for breast cancer even though there is substantial evidence that this group suffers from a disproportionate burden of breast cancer mortality (Sassi et al., 2006). Additionally, they are more likely to be diagnosed with breast cancer that has progressed to a more advanced stage and is clinically characterized by poor prognostic markers (i.e., estrogen receptor-negative) (Chlebowski et al., 2005; Acharya et al., 2008).

Environmental risk factors for breast cancer include lifestyle choices such as smoking, alcohol use, obesity, reduced or no physical activity, high-red meat diet, hormone replacement therapy, and parity (Mustacchi, 1961; MacMahon et al., 1970; Cerhan et al., 1998; Cho et al., 2006; Sillanpaa et al., 2007; Vona-Davis et al., 2007; Zhang et al., 2007). With respect to environmental exposures, animal studies conducted by the National Toxicology Program have found an association between exposure to 48 different chemicals and the development of mammary tumors (National Toxicology Program, 2007a). However, studies demonstrating a causal relationship between chemicals and breast cancer in humans have been contradictory. Additionally, identifying the critical periods of exposure to chemicals which are hypothesized to confer the greatest risks for cancer has been challenging. To date, the majority of the evidence associating chemical exposure to human breast cancer has been obtained from occupational studies (Brody and Rudel, 2003). A 2001 study by Davis et al. found that night shift workers of having an increased risk of breast cancer which has led to a suggested role for melatonin;

the naturally-occurring hormone that serves as a critical antioxidant and provides protection against DNA damage (Davis et al., 2001; Schernhammer et al., 2001).

Familial history of breast or any other type of cancer confers a risk for cancer diagnosis. Females who carry mutations in the BRCA1 and BRCA2 genes have a 20% increase in risk of developing breast cancer during their early 30s to 63% after age 70 (Claus et al., 1998). In this same study, by Claus 66% of BRCA mutation carriers reported a family history of breast cancer. However, it is estimated that 8 out of 9 women who develop breast cancer do not have an affected first-degree relative (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). This suggests a potent role of the environment or gene–environment interactions in the majority of breast cancer cases.

The genotype of the breast cancer patient affects not only their susceptibility to environmental insults but their response to treatments. Genetic mutations in the PTEN gene have been shown to increase the risk of resistance to trastuzumab (i.e., Herceptin) therapy which counters the aberrant cell proliferation activity of the HER2/neu protein that is seen in 15–22% of early stage breast cancers (Berns et al., 2007). Assessments of mutations in the tumor suppressor gene, p53, are considered powerful prognostic markers for poor outcomes among "node-negative" breast cancer patients (Silvestrini et al., 1993). A 2007 study found that mutations in 2 different alleles of the cell-cycle checkpoint kinase (CHEK2) gene conferred an elevated risk of breast cancer (Bell et al., 2007). Among female breast cancer patients, the P85L variant was more frequent among African–Americans and Ashkenazi Jews while the 1100delC was observed more frequently only among African–Americans. Female relatives of patients with the disease ataxia-telangiectasia are often carriers of mutations in the ataxia-telangiectasia (ATM) gene (i.e., the gene responsible for the disease) and consequently are at significant risk for breast cancer before the age of 60 (OR = 2.9) and after (OR = 6.4) (Athma et al., 1996; Thompson et al., 2005).

With respect to a gene-environment role in breast cancer, the NAT2, and cytochrome-p450 (CYP) genes each play a critical role in the production of enzymes necessary for detoxification of the compounds found in tobacco smoke and the metabolites of alcohol (Klaassen, 2001). Sillanpaa et al. found that among women smokers, the risk for breast cancer was increased by the presence of a SNP in the CYP1B1 gene or the combination of SNPs in both the NAT2 and CYP1A1 genes (Sillanpaa et al., 2007). In 2004, a study found that among Connecticut women exposed to environmental polychlorinated biphenyls (PCBs), a known endocrine disruptor, the risk for breast cancer was marginally increased (OR = 1.5) (Zhang et al., 2004). Additionally, Zhang et al. found that among women who were exposed to PCBs and who also possessed a specific SNP in the CYP1A1 gene m2 variant, the risk for breast cancer doubled (OR = 2.1) with the risk quadrupling (OR = 4.1) among post-menopausal women. This finding is significant since the CYP1A1 m2 variant is believed to be present in approximately 12% of the White female population. Studies such as these have a substantial public health impact since many endocrine disruptors are known to persist for long periods of time in the environment. This is complicated by the fact that the global distribution of the variant alleles in candidate genes for breast cancer is not yet known.

### 2.4.3 Colorectal Cancer

Currently, death due to colorectal cancer is the third leading cause of cancer-related mortality in the Western world (National Cancer Institute, 2007c). The occurrence of this cancer before the age of 50 is about equal between men and women. However, after age 50 men become increasingly vulnerable. Colorectal cancer incidence and mortality has steadily decreased for most groups, except American Indians and Alaskan Natives, while rates among Whites and African–Americans remain the highest. Recent studies have found significant variation among race and ethnic groups with respect to stage of diagnosis and risk for mortality (Chien et al., 2005; Alexander et al., 2007). The primary contributing factors to these disparities are patient education and access to preventive screening.

The environmental risk factors for colorectal cancer are reflective of the "Western lifestyle". These risk factors include diet, alcohol consumption, smoking, physical activity, and obesity. Moore et al. found that among subjects enrolled in the Framingham cohort, obesity defined by a BMI > 30 conferred a 1.5-fold risk among those 30–54 years of age and 2.4-fold risk among subjects age 55–79 (Moore et al., 2004). Additionally, the risk conferred by a high BMI was greater among males when compared to females. These authors also found that a large waist circumference (> 39 inches) conferred at least a 2-fold risk for colorectal cancer with the greatest risk observed among sedentary older and younger adults (relative risks = 3.0–4.4, respectively). More recently, Chia et al. found that an elevated serum level of the obesity biomarker, leptin, was associated with a 3.3-fold risk for colorectal among men (Chia et al., 2007). A 2005 multinational European cancer study found that both male and female who frequently consumed red meat were at an increased risk for colorectal cancer (OR = 1.35) with the risk increasing after the age of 50 (OR = 1.71) (Norat et al., 2005). Conversely, a diet rich in fish conferred a reduced risk of cancer before the age of 50 (OR = 0.69 vs. 1.5) and after the age of 50 (OR = 1.28 vs. 2.4).

In a study among Finnish men 42–61 years of age at baseline, heavy weekly consumption of alcohol (14 servings of beer or 16 servings of liquor) conferred a 3.5-fold lifetime risk for diagnosis of colorectal cancer (Toriola et al., 2008). A recent longitudinal study among adults 50–71 years of age at baseline observed an inverse linear correlation between exercise frequency (≥ 5 times a week) and colon cancer (OR = 0.79) among (Howard et al., 2008) men. Additionally, men who were sedentary (≥ 9 h a day watching television or videos) were at a 1.6-fold increased risk for colon cancer. This risk is further increased by smoking status and affects not only the incidence but the aggressiveness of the tumor (Botteri et al., 2008).

In addition to the evidence identifying elements of the "Western lifestyle" as independent risk factors for colorectal cancer, recent studies have found that this risk is further modified by an individual's genotype. The evidence supporting a role for the interaction between diet and SNPs in the CYP2E1 gene was published in 2002 (Le Marchand et al., 2002). The authors found that individuals who were carriers of a functional SNP in the CYP2E1 gene had a baseline elevated

risk for developing rectal cancer. This risk was increased 2- to 3-fold among those who consumed a diet that was rich in either red meat or processed meats or ate pickled products. These findings are significant since the pro-carcinogenic *N*-nitrosamine compounds, which are found in both types of meats, are bio-activated by the CYP450 enzymes resulting in DNA adduct formation. Thus, it is biologically plausible that a SNP which results in an increased induction of these CYP450 enzymes accompanied by a diet rich in *N*-nitrosamine compounds would result in a significant risk of developing colorectal cancer. The evidence supporting the risk imposed by cigarette smoking and alcohol consumption suggests a significant role of SNPs in the DNA repair genes XRCC1 and XDP. In 2005, Stern et al. found that among patients diagnosed with colorectal cancer and functional SNPs in the XRCC1 genes, a history of "ever smoking" conferred a significant risk for colorectal cancer (OR = 2.9) (Stern et al., 2006). Additionally, among individuals with SNPs in the XDP gene, a statistically significant contribution (OR = 2.5) from alcohol consumption among "ever drinkers" when compared to "never drinkers" was observed.

In an environment of robust cell cycle activity, such as the digestive system, there are many factors that contribute to the homeostasis that averts neoplastic growth. There is growing evidence of the role that methyl-donor nutrients (i.e., folic acid-containing foods) play in chemoprevention thus a diet that is rich in grains, fruits, and vegetables should be intuitive. Additionally, reduced intake of red meats and other foodstuffs which are known to induce the generation of DNA adducts or free radicals is currently advocated by public health professionals especially since the population distribution of functional SNPs in DNA repair genes is not yet known.

### *2.4.4 Esophageal Cancer*

Since the 1970s, the growth in the incidence and mortality rate of esophageal cancer has exceeded the annual growth rate of every other cancer (Brown and Devesa, 2002; Pickens and Orringer, 2003). In the US, the increase in the incidence of esophageal cancer has been greatest among White males but the mortality rates among African–American males remains higher even though the diagnosis among this group has declined steadily over the last 15 years (Blot and McLaughlin, 1999; National Cancer Institute, 2007d). There has been some question about the contribution of improved diagnostics to the increase in esophageal cancer. However, a 2005 study found that when adjusted for the increased use of endoscopies, the incident rate and the primary site of diagnosis (the lower third of the esophagus) has remained steady since 1975 (Pohl and Welch, 2005). Risk factors for esophageal cancer include reflux disease (Barrett's esophagus), obesity, extremely low weight, and low fruit and vegetable consumption (Morris Brown et al., 1995; Engel et al., 2003; Samanic et al., 2006; Corley et al., 2008). More recently, the risk conferred role by alcohol consumption has come under greater scrutiny.

The association between esophageal cancer and alcohol consumption has been studied extensively in Japanese men (Miyazaki et al., 2002; Sakata et al., 2005; Ishikawa et al., 2006). It has been reported that heavy alcohol consumption and death due to alcohol-associated diseases has increased dramatically among Japanese males (Makimoto et al., 2000). Adding to the increased prevalence of this risk factor is the identification of SNPs, amongst Japanese men, in the genes encoding for two enzymes that are critical for detoxifying ethanol; alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) (Tanaka et al., 1996, 1997). Researchers have examined the association between the polymorphisms in the ADH and ALDH genes among Eastern Asian men and the risk of being diagnosed with esophageal cancer (Yang et al., 2005; Chen et al., 2006). Yang et al. found an increased risk of esophageal cancer among Japanese men who possessed an ALDH polymorphism and were either moderate drinkers (OR = 1.88) or heavy drinkers (OR = 4.62). Chen et al. also found that the risk of esophageal cancer was further modified by the lifetime drinking (i.e., > 300–350 cc. of beer for 20 consecutive years) resulting in a 20-fold increase among those with an ADH gene polymorphism and 30-fold increase among those with an ALDH gene polymorphism.

Although the majority of gene–environment interaction studies, with respect to esophageal cancer, have been conducted among "frequent/heavy drinkers" (i.e., 2 six packs of beer/day), the risk conferred from a susceptible genotypes among other categories of drinkers is not known. These include "binge-drinkers", younger vs. older drinkers and those who drink alcoholic beverages with higher alcohol content (i.e., 12% ethanol in hard liquor vs. 5% ethanol in beer). Furthermore, the degree of penetrance or the population distribution of the candidate genes for esophageal cancer remains unknown. Such information could have a dramatic effect population health since the 5-year survival rate of this cancer is 20–25%.

### *2.4.5 Leukemia*

Leukemia is a cancer that originates in the bone marrow and results in a large number of blood cells to be produced. Although this cancer occurs more often in adults than in children (10 to 1), is the most common pediatric cancer and is the leading cause of mortality among children < 14 years of age. This cancer is most likely to be diagnosed in White males although the mortality rates between Whites and African-Americans are comparable. Leukemia is also divided into four types; acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML). ALL is the most common type of leukemia in children while AML, primarily found in older adults, is the most common among adults. Epidemiologic surveillance studies have reported geographic variation in the incidence of leukemia (i.e., higher incidence in wealthier, developed countries) but the identification of population-attributable factors is lacking.

Environmental exposures that have been identified as risk factors for leukemia include ionizing radiation and benzene. Benzene is used a solvent in the production of many chemicals and is found in gasoline due to its natural occurrence in crude oil. The current classification of benzene as a known carcinogen has existed since 1980 and is based on various human studies (Savitz and Andrews, 1997; National Toxicology Program, 2005b). Additionally, the potential human health threat of benzene exposure (i.e., inhalation or ingestion) has been recognized by several federal agencies including the Department of Health and Human Services, the Environmental Protection Agency, the Department of Transportation, and the Occupational and Safety Hazard Administration. At the cellular level, toxicity is caused by the production of reactive oxygen species as benzene is being metabolized by CYP450 enzymes (Agency for Toxic Substances and Disease Registry, 2005). Tissue-specific targets of the reactive oxygen species appear to be the hematopoietic cells and the bone marrow tissue (Ross et al., 1996).

Environmental exposure to ionizing radiation occurs in everyday life. Although in small amounts, sources of environmental radiation include those which are naturally-occurring such as radon which is found in granite and coal and those from man-made sources such as TVs, X-rays, and cigarette smoke (National Institutes of Health, 2000). As with benzene, a significant portion of the scientific data that established a relationship between radiation exposure and leukemia has been obtained from human studies (Lewis, 1957; Lewis et al., 1957). Since ionizing radiation is known to induce DNA damage, it is logical to assume that any health effects would be a function of the duration of the dose. However, for an individual whose DNA repair machinery is compromised (i.e., SNPs in essential detoxifying and/or DNA repair genes), the risk of developing leukemia due to environmental exposures to ionizing radiation would be expected to be higher.

Recent studies have identified candidate genes that confer an increased risk for developing acute myeloid leukemia. Majumdar et al. reported a significant risk of developing AML among individuals who were carriers of the GSTM1 null genotype (OR = 3.25), or were homozygous for polymorphisms in the NAT2 (OR = 3.19) or CYP1A1 2A (OR = 4.88) (Majumdar et al., 2008). Smith et al. found that the frequency of diminished or no NQO was higher among their cohort of patients who had been diagnosed with leukemia (OR = 1.49) when compared to matched controls who did not have leukemia (Smith et al., 2001). Polymorphisms in the folate metabolizing genes, 5,10-methylenetetrahydrofolate reductase, serine hydroxymethyltransferase, and thymidylate synthase have been reported to confer protection against developing ALL in adults (Skibola et al., 1999, 2002). Since the cells involved in leukemia are characterized by a high turnover rate, the reduced bioavailability of folate which results in an increased risk of DNA damage due to an accumulation of uracil in the DNA is significant.

The interest in fetal or *in-utero* programming for adult diseases has included studies interested in assessing the relationship of maternal exposure to radiation or benzene during pregnancy and the development of ALL in the offspring. Most

of these investigations have focused on exposures incurred within the occupational setting. Infante-Rivard et al. found that high occupational exposure to extremely low frequency magnetic fields (i.e., sewing machine and electronic factories), was associated with a two-fold increase in risk of ALL, the most common type of pediatric leukemia, in the offspring (Infante-Rivard and Deadman, 2003). An earlier study by this same group found an increased risk of developing ALL among children who possessed SNPs in the CYP1A1, CYP2D6, GSTT1, and GSTM1 genes and had been exposed to insecticides, rodenticides, or pesticides *in-utero* or during infancy (Infante-Rivard et al., 1999). During this study, the researchers found that the incidence of ALL was significantly related to *in-utero* or early childhood exposure to multiple products and SNPs in the CYP1A1 gene. When examining the risk for ALL conferred from the child's genotype, they observed a significant interaction between outdoor skin repellents exposures, *in-utero* (OR = 5.5) or in childhood (OR = 3.6), possessing the CYP1A1 ml variant, and ALL. When examining the influence of the CYP1A1 m2 variant, a significant risk for ALL was found among those possessing this allele who had been exposed *in-utero* to ant, roach, or wasp pesticides. However, even with such evidence, the mechanisms that would explain the effects from *in-utero* exposures radiation or chemicals on fetal development of biotransformation and DNA repair enzymes remains unknown.

Different studies have found a gene–gene interaction in the risk for ALL which highlights the importance of the interactions between SNPs at various loci. In their study, Canalle et al. examined the risk conferred by polymorphisms in the genes that encode for both Phase I (CYP1A1, and CYP2E1) and Phase II (GSTM1, GSTT1, GSTP1) detoxifying and metabolizing enzymes (Canalle et al., 2004). Initially, they observed an increase in risk conferred by a solo and rare SNP in the GSTP1 gene (OR = 2.7). However, a synergistic effect on the risk for developing ALL was observed among individuals whose possessed multiple variants in the CYP1A1, CYP2E1, GSTM1, and GSTP1 genes (OR = 10.2). Gene–gene interaction in the risk for ALL has also been found in studies examining the relationship between ALL and SNPs in the CYP2E1, MPO and NQO1 genes. A synergistic effect on the risk of ALL was found amongst individuals who carried the wild-type MPO allele and the CYP2E1 and NQO1 variants (OR = 5.4) (Krajinovic et al., 2002). Sinnett et al. have also examined the interaction between the genes involved in the Phase I (i.e., CYP1A1, CYP2D6) and Phase II (i.e., GSTM1, GSTT1, NAT1 and NAT2) xenobiotic biotransformation pathways (Sinnett et al., 2000). Although an elevated risk was conferred by the individual variants (OR = 1.6–1.7), the risk increased with the simultaneous presence of SNPs in CYP450 and GST genes (OR = 2.6). Additionally, the risk increased in slow acetylators who also possessed SNPs in the NAT genes (OR = 3.3).

With the unknown population distribution of genes critical for protection against oxidative stress and repair of DNA damage coupled with the ubiquitous presence of benzene in our environment (i.e., gasoline, environmental tobacco smoke), the effect on cancer-related population health risk may yet to be realized.

### *2.4.6 Liver Cancer*

Hepatocellular carcinoma (HCC) or liver cancer is an aggressive cancer with a poor 5-year survival rate. This statistic may explain why HCC is the third leading cause of cancer-specific mortality across the globe (Parkin et al., 2005). In the US, the incidence and mortality rate of liver cancer is higher among men when compared to women and among Hispanics, Asian–Americans and Pacific Islanders when compared to African–Americans and Whites (National Cancer Institute, 2007e). Global population studies have also found a higher prevalence of liver cancer among Asian and sub-Saharan African populations which is consistent with the geographic region's high prevalence of Hepatitis B and C (Raza et al., 2007). Individuals who have been diagnosed with heritable hemochromatosis, a metabolic disorder resulting in "iron-overload", are also at an increased risk of developing liver cancer.

Population-attributable risk factors such as chronic liver infections (i.e., Hepatitis A, B, or C), heavy alcohol consumption, and regular ingestion of aflatoxin (a compound found in nuts) explain the majority of new cases of liver cancer around the world. Alfatoxin, a naturally-occurring mycotoxin produced by certain *Aspergillus* species, is found in crops such as nuts, oilseeds, and cereals which are main diet staples in many Asian and African countries. The risk conferred from Hepatitis B virus (HBV), Hepatitis C virus (HCV), or aflatoxin ingestion is due to their effects on the genes involved in DNA damage repair (Pang et al., 2008). The HBV, a DNA virus, is characterized by the production of the viral protein, HBx, which subsequently reduces the bioavailability of p53. The HCV, an RNA virus, also inhibits cellular apoptosis via the production of the HCV core proteins, NS3 and NS5A (Ghosh et al., 1999; Marusawa et al., 1999; Kwun et al., 2001). NS3 and NS5A promote aberrant cell growth by inhibiting the activity of other proteins involved in apoptosis such as p21 (WAF), Fas, and TNF-α. The ingestion of alflatoxin also induces mutations in the p53 gene (Shen and Ong, 1996; Liu et al., 2008). This may explain the disproportionate burden of liver cancer in Asian populations where HBV is endemic and daily nut consumption is high.

The lack of a diagnostic biomarker for liver cancer contributes to the poor 5-year survival rate (Parkin et al., 2005). Since the 1970s, diagnosis of liver cancer has relied on the serological detection of α-fetoprotein (AFP), a non-specific liver protein that has a high false-positive rate since its is also observed in those with cirrhosis and hepatitis (Taketa, 1990). To date, the identification of preventive biomarkers for use in the screening of "at-risk" individuals for liver cancer has progressed slowly. However, research that seeks to identify predictive biomarkers (i.e., cytokine profiles) that characterize the chronic inflammation seen in liver cancer (especially in the presence of cirrhosis or infection) has made significant strides in recent years. This is significant since persistent inflammation is also characterized by a high turnover of cells which in turn increases the risk of malignant transformation and would explain why in the absence of surgical resection or a liver transplant, a poor prognosis accompanies a diagnosis of liver cancer (Moss and Blaser,

2005; Mazzanti et al., 2008). Recent studies at the National Cancer Institute have discovered a unique cytokine profile of the T-helper lymphocyte cells found in the cancerous liver microenvironment (Jia et al., 2007). Wang et al. identified the GPC3 gene that encodes for extracellular protein glypican 3 which is detectable in serum and elevated in patients with liver cancer. Other studies have found elevated levels of PEG10 and MDK in the sera of liver cancer patients (Kato et al., 2000). Future studies that seek to identify individuals who are genetically predisposed to the overproduction of these critical proteins (i.e., polymorphisms in the GPC3, PEG10, and/or MDK genes) would have a significant impact on global morbidity and mortality rates that are attributed to liver cancer.

As with other cancers, there has been an increased focus on the synergy between cigarette smoking and polymorphisms in the NAT2 gene among individuals who have chronic liver disease (i.e., cirrhosis, Hepatitis infection). Tobacco use has been shown to act synergistically with alcohol use in the development of liver cancer (Marrero et al., 2005). Polymorphisms in the NAT2 gene have been found to increase the risk of liver cancer among smokers and smokers with Hepatitis B (Yu et al., 2000; Farker et al., 2003). With respect to aflatoxin ingestion, the environmental insult is induced by the metabolite, aflatoxin 8,9 epoxide, which is detoxified by epoxide hydrolase (EPHX) and GSTM1 (Tiemersma et al., 2001). Tiemersa et al. has reported that among populations who consume high daily levels of peanut butter and who also report high rates of Hepatitis B infection, there is a significant contribution from the GSTM1 null or EPHX heterozygous genotype towards the risk of liver cancer.

Liver cancer is unique in that its incidence is primarily attributed to lifestyle factors. With the increase of other population-attributable factors such as obesity and consumption of processed foods and the continued lack of an early diagnostic or prognostic biomarker, liver cancer will likely be categorized an emerging public health threat within the next decade.

### *2.4.7 Lung Cancer*

Lung cancer continues to be the leading cause of cancer-related deaths among men and women in the US. Although the mortality rate for males has declined, the mortality rate for females has remained steady (National Cancer Institute, 2007f). Lung cancer is characterized by a lengthy, asymptomatic latent period (i.e. >10 years) and poor prognosis. The lack of an early diagnostic tool is an additional factor for lung cancer mortality (Godley et al., 2003). Although regularly CT scans have been suggested for those "at risk", it is believed that the benefit of such would be overshadowed by the cost of these services and the increased risk for other cancers conferred from radiation exposure (Bach et al., 2007).

Environmental risk factors for lung cancer include a family history of lung cancer, smoking, second-hand tobacco smoke, exposure to naturally-occurring radon gas, and occupational exposure to asbestos, silica, and chromium (Alberg and Samet, 2003; Etzel et al., 2003; Alberg et al., 2007). Interestingly, public and

occupational health has made tremendous strides in increasing awareness of and reducing exposures to environmental risk factors. However, lung cancer incidence and associated mortality continues to be a significant health issue in the US. Furthermore, the differential lung cancer incidence among those who are equally exposed to environmental risk factors strongly suggests a key role for individual genomic variability.

Genes in which functional SNPs have been identified to confer risk for lung cancer include the following; CYP450, EPHX, MPO, NQO, and GST. In studies where no smoking history was available or subjects were never smokers, a genetic contribution was observed from the CYP1A1 alone or GSTM1 variants in the presence of the CYP1A1 SNP (Taioli et al., 1998; Hung et al., 2003; Taioli et al., 2003; Raimondi et al., 2005). Two separate studies have described a relationship between SNPs in the EPHX gene and lung cancer risk in non-smokers. One study found an increased risk for lung cancer among non-smokers conferred from a SNP in the EPHX gene but another observed a protective effect from the interaction of SNPs in both the EPHX and GSTM1 genes (Zhou et al., 2001, 2002). Studies have found elevated levels of NQO in cancer lung cancer tissue of non-smokers as well as the increased, but statistically insignificant, prevalence of SNPs in the NQO gene (Schlager and Powis, 1990; Alexandrie et al., 2004). The findings presented in this paragraph are especially relevant since these candidate genes play key roles in detoxifying chemicals, including polycyclic aromatic hydrocarbons (a primary component of cigarette smoke and air pollution). Additionally, these findings suggest that SNPs in these genes affect the stoichiometric balance that is required to efficiently metabolize and detoxify numerous toxicants.

Of all the cancer risk factors identified to date, cigarette smoking continues to be the most frequently cited. A history of cigarette smoking is indicated in 85–90% of all lung cancers. However, the evidence demonstrating an increased risk conferred by polymorphisms in the genes that detoxify carcinogens found in cigarettes has been inconsistent. In a study to examine the effect of mutations in the CYP1A1 gene, Ishibe et al. only observed a significant effect among light smokers (<30 pack years), no effect amongst heavy smokers and no modification on these effects by race (i.e., African–American) (Ishibe et al., 1997). Another study found a higher expression of CYP1A1 in lung tissue of ex-smokers when compared to current and non-smokers ($p < 0.007$) (Kim et al., 2004). The enzyme EPHX has a critical detoxifying role with respect to carcinogens found in cigarettes but its effect on lung cancer has been examined in only few studies. In an interesting study examining the effect of SNPs in the EPHX gene among Mexican-Americans, Wu et al. found an increase risk of lung cancer among Mexican-Americans (OR = 3.6) with an even higher risk in the group < 65 years of age (OR = 7.4) (Wu et al., 2001). Although Hispanics have lower rates of lung cancer, this study suggests the contribution from a non-traditional source of environmental exposures; that from ethnic acculturation (i.e., the Western lifestyle). Wenzlaff et al. found that among their cohort of non-smokers who reported heavy exposure to environmental tobacco smoke (i.e., > 20 years of ETS), those possessing the GSTM1 null genotype had more than a two-fold risk for lung cancer. Furthermore, this genotype acted synergistically with mutations

in one or both alleles of the GSTP1 conferred a four-fold lung cancer risk (Wenzlaff et al., 2005). This is significant since the majority of non-smoking lung cancer patients report being exposed to ETS. A puzzling aspect of the relationship between smoking and lung cancer is the fact that not all smokers develop lung cancer. Prior to the knowledge of genomic risk factors, variability in response to carcinogens was suspected of being a function of the variability of population-attributable risk factors (i.e., diet, use of hormones, alcohol consumption). However, studies examining the differential expression of MPO have found that individuals, especially smokers, who possess a SNP in this gene are actually protected from developing lung cancer (Schabath et al., 2002; Taioli et al., 2007). However, caution must be exercised in interpreting these results as a "license to smoke" since this observation has only been observed in lung cancer studies while smoking is well-established as an independent risk factor for cancer and other chronic diseases. The NAT1 "fast" genotype has been observed to confer an increased risk of lung cancer (OR = 1.92) but not the NAT2 "slow" genotype (Wikman et al., 2001). However, when this study group was stratified by smoking status, the NAT1 "fast" genotype was observed more frequently among individuals diagnosed with small cell carcinoma and among those > 60 years of age. Since mutations in the enzyme, NQO, result in reduced bioavailability of this enzyme, researchers have been interested in whether this reduction in enzyme activity results in reduced bio-activation of carcinogens thus reducing the risk for lung cancer. However, the results from such hypothesis-driven studies have been contradictory. Xu et al. found that former smokers possessing the NQO1 C/T genotype had almost a four-fold risk of lung cancer (Wikman et al., 2001). However, Lawson et al. found no relationship between smoking, the NQO1 C/T genotype, and lung cancer (Lawson et al., 2005). Interestingly, a small cohort study found that the wild-type NQO1 (i.e., normal NQO carcinogen-activating activity) was more prevalent in African Americans who had been diagnosed with lung cancer suggesting that mutations in this gene may explain the increased incidence of cancer among African-Americans (Wiencke et al., 1997).

Contrary to the gene–environment interactions cited in other cancers, the role of exposure to tobacco smoke appears to be the primary determinant of lung cancer development. Even more discouraging is the fact that the genes of interest have a very wide applicability in the metabolism and biotransformation of toxicants (i.e., they act on a wide variety of agents). As the results of the HapMap project are incorporated into prevention and practice, it is likely that haplotype characterization, in combination with environmental exposure assessment, will provide the tools for predicting and reducing lung cancer morbidity and mortality.

### *2.4.8 Melanoma*

The skin is the largest organ in the human body. Melanoma is the cancer that forms in the skin cells (melanocytes) which produces melanin, the pigment that gives skin its color (National Cancer Institute, 2008a). Melanoma is the deadliest form of skin

cancer even though there is a favorable prognosis when diagnosed early. Since the 1980s, the rate of melanoma diagnosis among Whites, the most susceptible group in the US, has increased from about 13/100,000–24.6/100,000 in 2005 (National Cancer Institute, 2008b). However, the mortality rate among all races and ethnicities has remained steady. The incidence of melanoma occurs more frequently in males when compared to females and more frequently among individuals > 50 years of age although it can occur at any age. Among individuals who are newly diagnosed with melanoma, only 10% report having a family history (American Cancer Society, 2008). Therefore, a majority of melanoma cases are likely attributed to other risk factors such as UV exposure, immuno-suppression, and seemingly benign skin conditions such as moles and freckles.

Heritability is a primary risk factor for melanoma. It is estimated that individuals with a mutations in any of the three highly-penetrant genes, p16, ARF, or CDK4, will incur a 67% lifetime risk of developing melanoma (Pho et al., 2006). However, carriers of these mutations account for less than ½ of all melanoma cases. Recent studies suggest that low penetrant genes may interact to modify the risk of melanoma. Two such genes are the BRAF and the MC1R. Mutations in the oncogene BRAF have been reported more frequently among males with a family history of melanoma (Meyer et al., 2003). This may partially explain why melanoma occurs more frequently in males than females. Other studies have found an increased frequency of BRAF mutations among melanoma patients who had intermittent sun exposure suggesting risk factors other than UV rays from sunlight may be involved in the development of this cancer (Maldonado et al., 2003). Another candidate gene is the MC1R gene which is responsible for skin pigmentation. The MC1R, a receptor found on the surface of melanocytes, is responsive alpha-melanocyte stimulating hormone (α-MSH) which is secreted during exposure to ultraviolet rays such as those found in direct sunlight. Some of the MC1R variants result in reduced or blunted expression of α-MSH and confer an increased risk for melanoma (Valverde et al., 1996). A recent report found that among individuals with no evidence of excessive sun exposure, and whose melanoma tumors developed in areas that were not continuously exposed to the sun (i.e., the trunk), the likelihood of mutations in both BRAF and MC1R were significantly greater (Landi et al., 2006). Additionally, this study found that the risk for melanoma conferred by a mutation in BRAF increased incrementally with the concomitant presence of one or two variant MC1R genes (OR for one copy = 2.8; OR for two copies = 5.7). Although the majority of study subjects were younger, the interaction of age with melanoma risk was not statistically significant ($p = 0.22$).

Although studies to date suggest divergent pathways in the development of melanoma, proactive measures to reduce exposure to environmental factors, such as direct sunlight, is encouraged. Furthermore, since the UV rays of sunlight induce DNA damage, risk factors that reduce DNA damage repair capability (i.e., cigarette smoking) should be avoided. Finally, since research on this cancer is still in its early stages, the "window of vulnerability" is not known. Thus, protection of young children from prolonged exposure to direct sunlight should always be avoided.

### *2.4.9 Occupational-Related Cancer*

Occupational settings have historically been the "gold standard" for confirming an environmental contribution to disease. A landmark study published in 1979 set the current standard for occupational exposure assessments which must now consider the contribution of individual genomic variability to the risk occupationally-related disease (Lower et al., 1979). Furthermore, understanding the contribution of an individual's genotype during the risk assessment process is crucial especially when estimating what amount of risk from occupational exposures that employers, regulators, and society are willing to accept in this risk/benefit "trade-off". The best example of a current dichotomy is the occupational exposure to asbestos.

Asbestosis is an occupationally-related disease attributed to the environmental exposure to asbestos. Asbestos, now recognized as a human carcinogen, had been used in the US since the 1800s in a variety of occupational settings ranging from insulation in houses and buildings to pads in vehicle brakes and clutches (National Toxicology Program, 2005a; Agency for Toxic Substances and Disease Registry, 2007). In 1970, the use of asbestos began to be phased out culminating in an EPA ban on all new uses in 1989. However, its established uses were allowed to continue which includes many buildings and homes built before 1970 and many vehicles on the road today. A growing public health concern is the use of personal protective equipment among the workforce that may be regularly exposed to asbestos, especially demolition workers in older, urban cities. More recently, protecting disaster, recovery, and first-responder teams from asbestos exposure has become an emerging occupational public health issue, especially after the attacks on September 11, 2001 (Landrigan et al., 2004; Johnson et al., 2005).

As with other diseases, polymorphisms in the GSTM1 and NAT2 genes have been cited as risk factors for asbestosis (Hirvonen et al., 1996). This is significant since these enzymes modulate the cellular response to oxidative stress that occurs in the lung upon asbestos exposure. In the absence of such critical detoxifying enzymes, lung-scarring inflammation occurs with the subsequent replacement of viable lung tissue with fibrous tissue. Additionally, asbestosis has been firmly established as the leading risk factor for mesothelioma; a malignant cancer of the mesothelium. This cancer of the membranes lining the chest and abdominal cavities and surrounding internal organs is often asymptomatic for many years but once diagnosed, is difficult to control. A recent study conducted in Europe found that among Italian workers, NAT2 fast-acetylator genotype were significantly associated with malignant mesothelioma risk (OR = 1.9) (Neri et al., 2006). Additionally, the combination of a GSTM1-null and NAT2 fast-acetylator genotype further increased the risk of this aggressive cancer (OR = 2.4). It should be mentioned that in this same study, no effect was found among Finnish workers but this observation is hypothesized to be attributed to the source of asbestos. With respect to the contribution of smoking to asbestos-related cancer, the EPA's official risk advisory states a conferred risk from smoking and asbestos exposure towards lung cancer but not towards mesothelioma (Environmental Protection Agency, 2008).

As previously mentioned, the individuals at the most risk of exposure to asbestos are those in the construction and demolition trades. Although the US Occupational and Safety Hazard Administration has strict occupational standards regarding maximum personal exposure limits under normal circumstances, exposures are much harder to control during extraordinary situations, such as building collapses and fires. In spite of the evidence, the global use of asbestos in developing continues today even though studies have confirmed a relationship between its use the incidence of asbestosis, mesothelioma and lung cancer.

### *2.4.10 Pancreatic Cancer*

Currently in the US, pancreatic cancer is the fourth leading cause of cancer-related deaths. Both the incidence and mortality rate is about 50% higher in African–American males when compared to White males and it more frequently affects males of all races when compared to females (National Cancer Institute, 2007g). However, a recent study has reported that this disparity is explained by racial differences in cigarette smoking and prevalence of diabetes mellitus (Silverman et al., 2003). Trend analysis over the past two decades has shown very little improvement in either incidence or mortality rates in this cancer which has a poor prognosis since it is usually diagnosed at an advanced stage.

The evidence linking individual genetic variability and pancreatic cancer is sparse. The primary genetic risk factor for pancreatic cancer is hereditary pancreatitis. Chronic pancreatitis is a confirmed independent risk factor for pancreatic cancer. In 1996, a mutation in the cationic trypsinogen gene (PRSS1) was found to be common among individuals who suffered from a severe form of pancreatitis that onset during early adulthood (Whitcomb et al., 1996). More recently, this same group reported that through a multi-city linkage analysis, the frequency of this mutation in families affected by chronic pancreatitis was geo-specific in the US (i.e., more common in Minnesota, New York, Central Mid-Atlantic States, Kentucky, Ohio) (Applebaum-Shapiro et al., 2001). This study is a prime example of how genomics, in combination with the residential environment, may be able to address regional disparities in disease prevalence and severity. In addition to mutations in the PRSS1 gene, carriers of mutations in the BRCA genes are also at an increased risk of pancreatic cancer (Murphy et al., 2002; Hahn et al., 2003).

Cigarette smoking, some cigars, and heavy use of smokeless tobacco have been identified as leading environmental risk factors for pancreatic cancer (Silverman, 2001; Alguacil and Silverman, 2004). Additionally, smoking has been found to increase the risk conferred by other factors (i.e., family history, diabetes mellitus) for pancreatic cancer in women (Hassan et al., 2007). A study released by the National Cancer Institute found that among male smokers, the risk for pancreatic cancer was twice as high in those in the highest quartile of serum insulin levels when compared to those in the lowest quartile (Stolzenberg-Solomon et al., 2005). Although the "Western" diet and alcohol use have been shown to be significant risk factors for some cancers of the digestive system, this is not the case for pancreatic cancer

(Michaud et al., 2005). However, obesity in women (as measured by body mass index) has been identified as a significant risk factor for many cancers, including pancreatic (OR = 1.24) (Reeves et al., 2007). In 2002, an NIH-sponsored symposium on the risk factors for pancreatic cancer concluded that heavy alcohol use (> 15 g of alcohol/day or 10–11 drinks) was a leading cause of both chronic and acute pancreatitis, which are major risk factors for pancreatic cancer (American Pancreatic Association, 2003).

A recent study examined the utility of using NQO1 expression as a biomarker for pancreatic cancer among smokers (Lyn-Cook et al., 2006). NQO1 has been shown to be elevated in different types of cancer tissues. Thus, the investigators in this study were interested in the interaction of NQO1 expression and smoking among individuals with respect to pancreatic cancer. When compared to the NQO1 level in normal pancreatic tissue obtained from non-smokers, the NQO1 level in tissue from pancreatic cancer patients, who were also smokers, was six times higher. Although there are various mutations in this gene, there was no correlation between genotype and disease incidence. These findings suggest that although NQO1 normally protects cells from oxidative stress, in large quantities this enzyme may also be deleterious to the human body. Another candidate gene was examined for its interaction with heavy smoking (i.e., > 41 pack years) in conferring risk for pancreatic cancer (Duell et al., 2002). This study found that deletions in the GSTT1 gene increased the risk for pancreatic cancer five-fold in females and three-fold in males when compared "never" smokers with pancreatic cancer and this genotype. Interestingly, the risk of pancreatic cancer among carriers of this genotype was not significant in either never smokers or light smokers (i.e. < 40 pack years) demonstrating the powerful influence that cigarette smoking has on cancer risk.

### *2.4.11 Prostate Cancer*

Prostate cancer is currently the most frequent occurring cancer and the second leading cause of cancer-related mortality among men (National Cancer Institute, 2007h). Although overall rates of incidence and deaths have decreased due to increased screening for prostate cancer, these rates remain significantly higher among African–American men when compared to all other ethnic and race groups in the US (Godley et al., 2003; Cohen et al., 2006; Talcott et al., 2007). Additionally, this group of men is more likely to be diagnosed, via the prostate-specific antigen (PSA) test, at a later stage of disease development. This suggests disparities in both the quality of health care delivery to and health-seeking behavior among African-American men. Globally, geographic disparities have also been reported with rates higher among countries with high-fat diets and second-generation immigrants from developing countries to developed countries (Whittemore et al., 1995; Hayes, 2001). Therefore, the identification of relevant environmental risk factors has become increasingly urgent as the incidence of this preventable but deadly disease continues to rise.

To date, few studies have been able to determine a significant genetic contribution to disparities in prostate cancer incidence and mortality. With the evolution of genome-wide association studies, patterns of mutations at specific loci among patients diagnosed with prostate cancer have become evident but the clinical relevance of these biomarkers has yet to be determined (Xu et al., 2005; Thomas et al., 2008). A decade ago, shorter repeat lengths in one or both of the CAG and GGN sequences within the androgen receptor (AR) were found to confer a 1.5–2.0 times increased risk for developing prostate cancer among men 44–64 years of age (Stanford et al., 1997). At the time this finding was proposed to be a novel biomarker to predict the risk for prostate cancer, especially among African–Americans for whom the incidence is disproportionately higher when compared to other races and ethnicities. Despite numerous investigations, the most recent publication regarding this hypothesis found no association between shorter lengths between CAG and GGN repeats and the increased risk of prostate cancer among African-American men when compared to White men (Lange et al., 2008). Mutations in the BRCA genes are established risk factors for breast cancer. Interestingly, a recent study examining the risk conferred by BRCA for prostate cancer reported that males who are carriers of BRCA mutations are an increased risk ($p = 0.01$) for developing prostate cancer as well as having tumor histopathology (i.e., tumor grade) that is indicative of poor prognosis (Mitra et al., 2008). In 2006, a multi-city prostate cancer research group found that a mutation in a DNA segment on chromosome 8 found among men with African ancestry increased the risk of prostate cancer especially before the age of 70 years (Freedman et al., 2006). However, this variation only explained a fraction of early-onset cancer cases. Other studies have examined the risk conferred by SNPs in the PTEN, IGF-1, and ER-β genes which are observed in other cancers (Cheng et al., 2006; Haiman et al., 2006; Chen et al., 2007) but have been inconclusive in establishing a significant association with prostate cancer risk.

Although many studies have explored various risk factors for prostate cancer, scientific evidence has confirmed the significant contributions from the consumption of smoked meats, a diet high in animal fat and cigarette smoking (Hayes et al., 1999; Plaskon et al., 2003; Tang et al., 2007). These risk factors are also significant for other cancers such as pancreatic and liver. Among middle-aged men who smoke and who are carriers of the GSTM1-null genotype, the risk for developing prostate cancer increased linearly with the individual's pack years ($p < 0.007$) with the greatest risk observed for those with > 30 pack years (Agalliu et al., 2006). Another study found that sulforaphane, which is found in cruciferous vegetables, induces intracellular glutathione synthesis (a critical detoxification and anticarcinogenic process) in human prostate cancer cell lines. This finding provides a plausible mechanism by which a diet rich in leafy green vegetables is a protective factor against prostate cancer especially since prostate cancer cells are characterized by the loss of glutathione expression (Brooks et al., 2001). Polymorphisms in the NAT2 can result in either a slow- or fast-acetylator genotype. With respect to prostate cancer, the NAT2 slow acetylator genotype has been found to be more prevalent among these cancer patients (OR = 2.21) with the greatest prevalence among the patients who were smokers (OR = 3.8) (Hamasaki et al., 2003). Furthermore, the NAT2

slow-acetylator genotype was more frequent among patients with advanced stage of disease, metastasis, and high tumor grade. As a result of the accumulating evidence supporting a gene–environment interaction in the incidence and severity of prostate cancer, public health campaigns promoting prostate cancer screening and avoidance of the above-mentioned risk factors has increased substantially in recent years.

## 2.5 Summary

With the advent of molecular epidemiology and bioinformatics, biomedical researchers are now able to associate the presence of a quantifiable biomarker (i.e., genetic variants) with the risk of developing a specific disease. Furthermore, scientists can now characterize "genomic trends" (i.e., functional genomic variant frequencies) among diseased populations. Soon researchers will be able to translate these discoveries into improving population health and identify targets for disease prevention while furthering our understanding of the interactions of various physiological mechanisms.

The objective of this chapter was to discuss a select group of cancers for which there exists published evidence demonstrating a significant contribution from the environment towards cancer incidence, morbidity, and mortality. Here we have presented the evidence supporting the contribution to cancer development from several genes that play key roles in DNA damage repair or xenobiotic biotransformation. Additionally, we have presented a summary of evidence that for some cancers, the interaction between genetic polymorphisms (i.e., gene–gene interactions) confers an added risk as well. As initiatives such as the HapMap project progress, we may soon be able to estimate the global distribution of the critical polymorphisms thus "fine-tuning" the contribution of environmental exposures towards the development of cancer.

## References

Acharya, C. R., D. S. Hsu, et al. (2008). "Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer." JAMA **299**(13): 1574–1587.

Agalliu, I., W. J. Langeberg, et al. (2006). "Glutathione S-transferase M1, T1, and P1 polymorphisms and prostate cancer risk in middle-aged men." Prostate **66**(2): 146–56.

Agency for Toxic Substances and Disease Registry (2005). "Interaction profile for: Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX)." Retrieved May 14, 2008.

Agency for Toxic Substances and Disease Registry (2007). "Asbestos Toxicity: Who Is at Risk of Exposure to Asbestos?" Retrieved June 20, 2008, from http://www.atsdr.cdc.gov/csem/asbestos/risk2.html

Alberg, A. J., A. Kouzis, et al. (2007). "A prospective cohort study of bladder cancer risk in relation to active cigarette smoking and household exposure to secondhand cigarette smoke." Am J Epidemiol **165**(6): 660–6.

Alberg, A. J. and J. M. Samet (2003). "Epidemiology of lung cancer." Chest **123**(90010): 21S–49.

Alexander, D. D., J. Waterbor, et al. (2007). "African–American and Caucasian disparities in colorectal cancer mortality and survival by data source: an epidemiologic review." Cancer Biomark **3**(6): 301–13.

Alexandrie, A.-K., F. Nyberg, et al. (2004). "Influence of CYP1A1, GSTM1, GSTT1, and NQO1 genotypes and cumulative smoking dose on lung cancer risk in a Swedish population." Cancer Epidemiol Biomarkers Prev **13**(6): 908–14.

Alguacil, J. and D. T. Silverman (2004). "Smokeless and other noncigarette tobacco use and pancreatic cancer: a case-control study based on direct interviews." Cancer Epidemiol Biomarkers Prev **13**(1): 55–8.

American Cancer Society (2008). "What Are The Risk Factors for Melanoma?" Retrieved June 16, 2008, from http://www.cancer.org/docroot/CRI/content/CRI_2_2_2X_What_causes_melanoma_skin_cancer_50.asp?sitearea=

American Pancreatic Association (2003). "Mechanisms of alcoholic pancreatitis. Proceedings of the conference, Chicago, Illinois, USA, November 2002." Pancreas **27**(4): 281–355.

Anton-Culver, H., A. Lee-Feldstein, et al. (1993). "The association of bladder cancer risk with ethnicity, gender, and smoking." Ann Epidemiol **3**(4): 429–33.

Applebaum-Shapiro, S. E., R. Finch, et al. (2001). "Hereditary pancreatitis in North America: the Pittsburgh-Midwest Multi-Center Pancreatic Study Group Study." Pancreatology **1**(5): 439–43.

Athma, P., R. Rappaport, et al. (1996). "Molecular genotyping shows that ataxia-telangiectasia heterozygotes are predisposed to breast cancer." Cancer Genet Cytogenet **92**(2): 130–4.

Bach, P. B., J. R. Jett, et al. (2007). "Computed tomography screening and lung cancer outcomes." JAMA **297**(9): 953–61.

Bell, D., S. H. Kim, et al. (2007). "Genetic and functional analysis of CHEK2 (CHK2) variants in multiethnic cohorts." Int J Cancer **121**(12): 2661–7.

Bernal-Pacheco, O. and G. C. Roman (2007). "Environmental vascular risk factors: new perspectives for stroke prevention." J Neurol Sci **262**(1–2): 60–70.

Berns, K., H. M. Horlings, et al. (2007). "A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer." Cancer Cell **12**(4): 395–402.

Berry, G. and F. D. Liddell (2004). "The interaction of asbestos and smoking in lung cancer: a modified measure of effect." Ann Occup Hyg **48**(5): 459–62.

Blendon, R. J., T. Buhr, et al. (2007). "Disparities in health: perspectives of a multi-ethnic, multiracial America." Health Aff **26**(5): 1437–47.

Blot, W. J. and J. K. McLaughlin (1999). "The changing epidemiology of esophageal cancer." Semin Oncol **26**(5 Suppl 15): 2–8.

Botteri, E., S. Iodice, et al. (2008). "Cigarette smoking and adenomatous polyps: a meta-analysis." Gastroenterology **134**(2): 388–95.

Brody, J. G. and R. A. Rudel (2003). "Environmental pollutants and breast cancer." Environ Health Perspect **111**(8): 1007–19.

Brooks, J. D., V. G. Paton, et al. (2001). "Potent induction of phase 2 enzymes in human prostate cells by sulforaphane." Cancer Epidemiol Biomarkers Prev **10**(9): 949–54.

Brown, L. M. and S. S. Devesa (2002). "Epidemiologic trends in esophageal and gastric cancer in the United States." Surg Oncol Clin N Am **11**(2): 235–56.

CDC National Office of Public Health Genomics (2004, September 2007). "Public Health Genomics at CDC-Accomplishments and Priorities 2004." Retrieved Jan 14, 2008, from http://www.cdc.gov/genomics/activities/ogdp/2004/niosh.htm

Canalle, R., R. V. Burim, et al. (2004). "Genetic polymorphisms and susceptibility to childhood acute lymphoblastic leukemia." Environ Mol Mutagen **43**(2): 100–9.

Cerhan, J. R., B. C. Chiu, et al. (1998). "Physical activity, physical function, and the risk of breast cancer in a prospective study among elderly women." J Gerontol A Biol Sci Med Sci **53**(4): M251–6.

Chen, Y. J., C. Chen, et al. (2006). "Interactive effects of lifetime alcohol consumption and alcohol and aldehyde dehydrogenase polymorphisms on esophageal cancer risks." Int J Cancer **119**(12): 2827–31.

Chen, Y. C., P. Kraft, et al. (2007). "Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium." Cancer Epidemiol Biomarkers Prev **16**(10): 1973–81.

Cheng, I., D. O. Stram, et al. (2006). "Common genetic variation in IGF1 and prostate cancer risk in the Multiethnic Cohort." J Natl Cancer Inst **98**(2): 123–34.

Chia, V. M., P. A. Newcomb, et al. (2007). "Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk." Cancer Epidemiol Biomarkers Prev **16**(12): 2697–703.

Chien, C., L. M. Morimoto, et al. (2005). "Differences in colorectal carcinoma stage and survival by race and ethnicity." Cancer **104**(3): 629–39.

Chlebowski, R. T., Z. Chen, et al. (2005). "Ethnicity and breast cancer: factors influencing differences in incidence and outcome." J Natl Cancer Inst **97**(6): 439–48.

Cho, E., W. Y. Chen, et al. (2006). "Red meat intake and risk of breast cancer among premenopausal women." Arch Intern Med **166**(20): 2253–9.

Christiani, D. C. (2000). "Smoking and the molecular epidemiology of lung cancer." Clin Chest Med **21**(1): 87–93.

Claus, E. B., J. Schildkraut, et al. (1998). "Effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history." J Natl Cancer Inst **90**(23): 1824–9.

Cohen, J. H., V. J. Schoenbach, et al. (2006). "Racial differences in clinical progression among Medicare recipients after treatment for localized prostate cancer (United States)." Cancer Causes Control **17**(6): 803–11.

Collaborative Group on Hormonal Factors in Breast Cancer (2001). "Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease." Lancet **358**(9291): 1389–99.

Commonwealth Fund (2006). "Hispanic and African American Adults Are Uninsured at Rates One-and-a Half to Three Times Higher Than White Adults." Retrieved Jan 08, 2008, from http://www.commonwealthfund.org/usr_doc/DisparitiesReleaseFINAL7-26-06.pdf?section=4059

Corley, D. A., A. Kubo, et al. (2008). "Abdominal obesity and the risk of esophageal and gastric cardia carcinomas." Cancer Epidemiol Biomarkers Prev **17**(2): 352–8.

Davis, S., D. K. Mirick, et al. (2001). "Night shift work, light at night, and risk of breast cancer." J Natl Cancer Inst **93**(20): 1557–62.

Doty, M. M. and A. L. Holmgren (2005). "Health Care Disconnect: Gaps in Coverage and Care for Minority Adults." Commonwealth Fund pub. 941, Vol. 21. Retrieved Jan 08, 2008, from http://www.commonwealthfund.org/publications/publications_show.htm?doc_id=386220#areaCitation

Duell, E. J., E. A. Holly, et al. (2002). "A population-based, case-control study of polymorphisms in carcinogen-metabolizing genes, smoking, and pancreatic adenocarcinoma risk." J Natl Cancer Inst **94**(4): 297–306.

Engel, L. S., W. H. Chow, et al. (2003). "Population attributable risks of esophageal and gastric cancers." J Natl Cancer Inst **95**(18): 1404–13.

Environmental Protection Agency (2008). "Asbestos (CASRN 1332-21-4)." Integrated Risk Information System. Retrieved June 25, 2008, from Asbestos (CASRN 1332-21–4).

Etzel, C. J., C. I. Amos, et al. (2003). "Risk for smoking-related cancer among relatives of lung cancer patients." Cancer Res **63**(23): 8531–5.

Farker, K., U. Schotte, et al. (2003). "Impact of N-acetyltransferase polymorphism (NAT2) in hepatocellular carcinoma (HCC) – an investigation in a department of surgical medicine." Exp Toxicol Pathol **54**(5–6): 387–91.

Freedman, M. L., C. A. Haiman, et al. (2006). "Admixture mapping identifies 8q24 as a prostate cancer risk locus in African–American men." Proc Natl Acad Sci USA **103**(38): 14068–73.

Garcia-Closas, M., N. Malats, et al. (2006). "Genetic variation in the nucleotide excision repair pathway and bladder cancer risk." Cancer Epidemiol Biomarkers Prev **15**(3): 536–42.

García-Closas, M., N. Malats, et al. (2005). "NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses." The Lancet **366**(9486): 649–59.

Ghosh, A. K., R. Steele, et al. (1999). "Hepatitis C virus NS5A protein modulates cell cycle regulatory genes and promotes cell growth." J Gen Virol **80**(**Pt 5**): 1179–83.

Godley, P. A., A. P. Schenck, et al. (2003). "Racial differences in mortality among Medicare recipients after treatment for localized prostate cancer." J Natl Cancer Inst **95**(22): 1702–10.

Graham, R. R., W. Ortmann, et al. (2007). "Specific combinations of HLA-DR2 and DR3 class II haplotypes contribute graded risk for disease susceptibility and autoantibodies in human SLE." Eur J Hum Genet **15**(8): 823–30.

Grarup, N. and G. Andersen (2007). "Gene–environment interactions in the pathogenesis of type 2 diabetes and metabolism." Curr Opin Clin Nutr Metab Care **10**(4): 420–6.

Hahn, S. A., B. Greenhalf, et al. (2003). "BRCA2 germline mutations in familial pancreatic carcinoma." J Natl Cancer Inst **95**(3): 214–21.

Haiman, C. A., D. O. Stram, et al. (2006). "Common genetic variation at PTEN and risk of sporadic breast and prostate cancer." Cancer Epidemiol Biomarkers Prev **15**(5): 1021–5.

Hamasaki, T., H. Inatomi, et al. (2003). "N-acetyltransferase-2 gene polymorphism as a possible biomarker for prostate cancer in Japanese men." Int J Urol **10**(3): 167–73.

Harris, K. M., P. Gordon-Larsen, et al. (2006). "Longitudinal trends in race/ethnic disparities in leading health indicators from adolescence to young adulthood." Arch Pediatr Adolesc Med **160**(1): 74–81.

Harrison, R. (2004). Polycyclic aromatic hydrocarbons. In Current Occupational and Environmental Medicine. New York, NY, McGraw-Hill.

Hassan, M. M., M. L. Bondy, et al. (2007). "Risk factors for pancreatic cancer: case-control study." Am J Gastroenterol **102**(12): 2696–707.

Hayes, R. B. (2001). "Gene–environment interrelations in prostate cancer." Epidemiol Rev **23**(1): 163–7.

Hayes, R. B., R. G. Ziegler, et al. (1999). "Dietary factors and risks for prostate cancer among blacks and whites in the United States." Cancer Epidemiol Biomarkers Prev **8**(1): 25–34.

Heinrich, K. M., R. E. Lee, et al. (2008). "How does the built environment relate to body mass index and obesity prevalence among public housing residents?" Am J Health Promot **22**(3): 187–94.

Hirvonen, A., S. T. Saarikoski, et al. (1996). "Glutathione S-transferase and N-acetyltransferase genotypes and asbestos-associated pulmonary disorders." J Natl Cancer Inst **88**(24): 1853–6.

Howard, R. A., D. M. Freedman, et al. (2008). "Physical activity, sedentary behavior, and the risk of colon and rectal cancer in the NIH-AARP Diet and Health Study." Cancer Causes Control Nov;**19**(9): 939–53.

Hung, R. J., P. Boffetta, et al. (2003). "CYP1A1 and GSTM1 genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis." Carcinogenesis **24**(5): 875–82.

Infante-Rivard, C. and J. E. Deadman (2003). "Maternal occupational exposure to extremely low frequency magnetic fields during pregnancy and childhood leukemia." Epidemiology **14**(4): 437–41.

Infante-Rivard, C., D. Labuda, et al. (1999). "Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms." Epidemiology **10**(5): 481–7.

Ishibe, N., J. K. Wiencke, et al. (1997). "Susceptibility to lung cancer in light smokers associated with CYP1A1 polymorphisms in Mexican- and African–Americans." Cancer Epidemiol Biomarkers Prev **6**(12): 1075–80.

Ishikawa, A., S. Kuriyama, et al. (2006). "Smoking, alcohol drinking, green tea consumption and the risk of esophageal cancer in Japanese men." J Epidemiol **16**(5): 185–92.

Jia, H.-L., Q.-H. Ye, et al. (2007). "Gene expression profiling reveals potential biomarkers of human hepatocellular carcinoma." Clin Cancer Res **13**(4): 1133–9.

John, E. M., A. Miron, et al. (2007). "Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups." JAMA **298**(24): 2869–76.

Johnson, S. B., A. M. Langlieb, et al. (2005). "Rethinking first response: effects of the clean up and recovery effort on workers at the world trade center disaster site." J Occup Environ Med **47**(4): 386–91.

Kato, M., T. Shinozawa, et al. (2000). "Increased midkine expression in hepatocellular carcinoma." Arch Pathol Lab Med **124**(6): 848–52.

Khoury, M. J., R. Davis, et al. (2005). "Do we need genomic research for the prevention of common diseases with environmental causes?" Am J Epidemiol **161**(9): 799–805.

Khoury, M. J., R. Millikan, et al. (2004). "The emergence of epidemiology in the genomics age." Int J Epidemiol **33**(5): 936–44.

Kim, J. H., M. E. Sherman, et al. (2004). "Expression of cytochromes P450 1A1 and 1B1 in human lung from smokers, non-smokers, and ex-smokers." Toxicol Appl Pharmacol **199**(3): 210–19.

Klaassen, C. (2001). Casarett & Doull's Toxicology: The Basic Science of Poisons. New York, NY, McGraw-Hill.

Krajinovic, M., H. Sinnett, et al. (2002). "Role of NQO1, MPO and CYP2E1 genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia." Int J Cancer **97**(2): 230–6.

Kwun, H. J., E. Y. Jung, et al. (2001). "p53-dependent transcriptional repression of p21(waf1) by hepatitis C virus NS3." J Gen Virol **82**(Pt 9): 2235–41.

Lander, E. S., L. M. Linton, et al. (2001). "Initial sequencing and analysis of the human genome." Nature **409**(6822): 860–921.

Landi, M. T., J. Bauer, et al. (2006). "MC1R germline variants confer risk for BRAF-mutant melanoma." Science **313**(5786): 521–2.

Landrigan, P. J., P. J. Lioy, et al. (2004). "Health and environmental consequences of the world trade center disaster." Environ Health Perspect **112**(6): 731–9.

Lange, E. M., A. V. Sarma, et al. (2008). "The androgen receptor CAG and GGN repeat polymorphisms and prostate cancer susceptibility in African–American men: results from the Flint Men's Health Study." J Hum Genet **53**(3): 220–6.

Lawson, K. A., K. Woodson, et al. (2005). "Association of the NAD(P)H:quinone oxidoreductase (NQO1) 609C->T polymorphism with lung cancer risk among male smokers." Cancer Epidemiol Biomarkers Prev **14**(9): 2275–6.

Le Marchand, L., T. Donlon, et al. (2002). "Red meat intake, CYP2E1 genetic polymorphisms, and colorectal cancer risk." Cancer Epidemiol Biomarkers Prev **11**(10 Pt 1): 1019–24.

Lewis, E. B. (1957). "Leukemia and ionizing radiation." Science **125**(3255): 965–72.

Lewis, J. H., J. H. Burchenal, et al. (1957). "Studies of hemostatic mechanisms in leukemia and thrombocytopenia." Am J Clin Pathol **28**(5): 433–46.

Lichtenstein, P., N. V. Holm, et al. (2000). "Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland." N Engl J Med **343**(2): 78–85.

Liddell, F. D. (2001). "The interaction of asbestos and smoking in lung cancer." Ann Occup Hyg **45**(5): 341–56.

Liu, Z. M., L. Q. Li, et al. (2008). "Hepatitis B virus infection contributes to oxidative stress in a population exposed to aflatoxin B1 and high-risk for hepatocellular carcinoma." Cancer Lett **263**(2): 212–22.

Lower, G. M., Jr., T. Nilsson, et al. (1979). "N-acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark." Environ Health Perspect **29**: 71–9.

Lyn-Cook, B. D., Y. Yan-Sanders, et al. (2006). "Increased levels of NAD(P)H:quinone oxidoreductase 1 (NQO1) in pancreatic tissues from smokers and pancreatic adenocarcinomas: a potential biomarker of early damage in the pancreas." Cell Biol Toxicol **22**(2): 73–80.

MacMahon, B., P. Cole, et al. (1970). "Age at first birth and breast cancer risk." Bull World Health Organ **43**(2): 209–21.
Majumdar, S., B. C. Mondal, et al. (2008). "Association of cytochrome P450, glutathione S-transferase and N-acetyl transferase 2 gene polymorphisms with incidence of acute myeloid leukemia." Eur J Cancer Prev **17**(2): 125–32.
Makimoto, K., H. Oda, et al. (2000). "Is heavy alcohol consumption an attributable factor for cancer-related deaths among Japanese men?" Alcohol Clin Exp Res **24**(3): 382–5.
Maldonado, J. L., J. Fridlyand, et al. (2003). "Determinants of BRAF mutations in primary melanomas." J Natl Cancer Inst **95**(24): 1878–90.
Marrero, J. A., R. J. Fontana, et al. (2005). "Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma." J Hepatol **42**(2): 218–24.
Marusawa, H., M. Hijikata, et al. (1999). "Hepatitis C virus core protein inhibits Fas- and tumor necrosis factor alpha-mediated apoptosis via NF-kappaB activation." J Virol **73**(6): 4713–20.
Mazzanti, R., L. Gramantieri, et al. (2008). "Hepatocellular carcinoma: epidemiology and clinical aspects." Mol Aspects Med **29**(1–2): 130–43.
Meyer, P., C. Sergi, et al. (2003). "Polymorphisms of the BRAF gene predispose males to malignant melanoma." J Carcinog **2**(1): 7.
Michaud, D. S., H. G. Skinner, et al. (2005). "Dietary patterns and pancreatic cancer risk in men and women." J Natl Cancer Inst **97**(7): 518–24.
Mitra, A., C. Fisher, et al. (2008). "Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype." Br J Cancer **98**(2): 502–7.
Miyazaki, M., S. Ohno, et al. (2002). "The relation of alcohol consumption and cigarette smoking to the multiple occurrence of esophageal dysplasia and squamous cell carcinoma." Surgery **131**(1 Suppl): S7–S13.
Moore, L. L., M. L. Bradlee, et al. (2004). "BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults." Int J Obes Relat Metab Disord **28**(4): 559–67.
Morris Brown, L., C. A. Swanson, et al. (1995). "Adenocarcinoma of the esophagus: role of obesity and diet." J Natl Cancer Inst **87**(2): 104–109.
Moss, S. F. and M. J. Blaser (2005). "Mechanisms of disease: inflammation and the origins of cancer." Nat Clin Pract Oncol **2**(2): 90–7; quiz 1 p following 113.
Murphy, K. M., K. A. Brune, et al. (2002). "Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%." Cancer Res **62**(13): 3789–93.
Mustacchi, P. (1961). "Ramazzini and Rigoni-Stern on parity and breast cancer. Clinical impression and statistical corroboration." Arch Intern Med **108**: 639–42.
National Cancer Institute (2007a). "A snapshot of bladder cancer." Retrieved May 09, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/bladder.pdf
National Cancer Institute (2007b). "A snapshot of breast cancer." Retrieved May 09, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/breast.pdf
National Cancer Institute (2007c). "A snapshot of colorectal cancer." Retrieved June 03, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/colorectal.pdf
National Cancer Institute (2007d). "A snapshot of esophageal cancer." Retrieved May 9, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/esophageal.pdf
National Cancer Institute (2007e). "A snapshot of liver and bile duct cancers." Retrieved May 09, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/liver.pdf
National Cancer Institute (2007f). "A snapshot of lung cancer." Retrieved May 18, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/lung.pdf
National Cancer Institute (2007g). "A snapshot of pancreatic cancer." Retrieved June 24, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/Pancreatic.pdf
National Cancer Institute (2007h). "A snapshot of prostate cancer." Retrieved June 26, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/prostate.pdf

National Cancer Institute (2008a). "Skin Cancer." Retrieved June 17, 2008, from http://www.cancer.gov/cancertopics/types/skin/

National Cancer Institute (2008b). "Melanoma." Retrieved June 16, 2008, from http://www.cancer.gov/aboutnci/servingpeople/snapshots/melanoma.pdf

National Center for Biotechnology Information (2004). "Just the Facts: A Basic Introduction to the Science Underlying NCBI Resources." Retrieved May 20, 2008, from http://www.ncbi.nlm.nih.gov/About/primer/bioinformatics.html

National Heart Lung and Blood Institute (2006). "NHLBI to Launch Framingham Genetic Research Study." Retrieved June 09, 2008, from http://www.nhlbi.nih.gov/new/press/06-02-06.htm

National Human Genome Research Institute (2006). "Genetic Association Information Network Launched: Novel Public-Private Partnership Created to Unravel the Genetics Of Common Disease Through Whole Genome Association Studies." Retrieved June 09, 2008, from http://www.genome.gov/17516722

National Human Genome Research Institute (2007). "International HapMap Project." Retrieved June 03, 2008, from http://www.genome.gov/10001688

National Institutes of Health (2000). "What We know About Radiation-Fact Sheet." Retrieved May 14, 2008, from http://www.nih.gov/health/chip/od/radiation/

National Institutes of Health (2007). "The Genes, Environment and Health Initiative (GEI)." Retrieved June 10, 2008, from http://www.gei.nih.gov/

National Toxicology Program (2005a). "11th Report on Carcinogens." Eleventh Edition. From http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932

National Toxicology Program (2005b). "Benzene CAS No. 71-43-2." Report on Carcinogens Retrieved May 14, 2008 from http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s019benz.pdf

National Toxicology Program. (2007). "Chemicals Associated with Site-Specific Tumor Induction in Mammary Gland." Retrieved May 09, 2008, from http://ntp.niehs.nih.gov/index.cfm?objectid=E1D18034-123F-7908-7B2C2AE41B1F3778

Neri, M., E. Taioli, et al. (2006). "Metabolic genotypes as modulators of asbestos-related pleural malignant mesothelioma risk: a comparison of Finnish and Italian populations." Int J Hyg Environ Health **209**(4): 393–8.

Newbold, R. R., E. Padilla-Banks, et al. (2007). "Perinatal exposure to environmental estrogens and the development of obesity." Mol Nutr Food Res **51**(7): 912–17.

Newsom, S. W. (2006). "Pioneers in infection control: John Snow, Henry Whitehead, the Broad Street pump, and the beginnings of geographical epidemiology." J Hosp Infect **64**(3): 210–16.

Norat, T., S. Bingham, et al. (2005). "Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition." J Natl Cancer Inst **97**(12): 906–16.

Pang, R. W., J. W. Joh, et al. (2008). "Biology of hepatocellular carcinoma." Ann Surg Oncol **15**(4): 962–71.

Parkin, D. M., F. Bray, et al. (2005). "Global cancer statistics, 2002." CA Cancer J Clin **55**(2): 74–108.

Pho, L., D. Grossman, et al. (2006). "Melanoma genetics: a review of genetic factors and clinical phenotypes in familial melanoma." Curr Opin Oncol **18**(2): 173–9.

Pickens, A. and M. B. Orringer (2003). "Geographical distribution and racial disparity in esophageal cancer." Ann Thorac Surg **76**(4): S1367–9.

Plaskon, L. A., D. F. Penson, et al. (2003). "Cigarette smoking and risk of prostate cancer in middle-aged men." Cancer Epidemiol Biomarkers Prev **12**(7): 604–9.

Pohl, H. and H. G. Welch (2005). "The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence." J Natl Cancer Inst **97**(2): 142–6.

Poulsen, P., M. Esteller, et al. (2007). "The epigenetic basis of twin discordance in age-related diseases." Pediatr Res **61**(5 Pt 2): 38R–42R.

Prout, G. R., Jr., M. N. Wesley, et al. (2000). "Bladder cancer: race differences in extent of disease at diagnosis." Cancer **89**(6): 1349–58.

Raimondi, S., P. Boffetta, et al. (2005). "Metabolic gene polymorphisms and lung cancer risk in non-smokers. an update of the GSEC study." Mutat Res **592**(1–2): 45–57.
Raza, S. A., G. M. Clifford, et al. (2007). "Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review." Br J Cancer **96**(7): 1127–34.
Reeves, G. K., K. Pirie, et al. (2007). "Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study." BMJ **335**(7630): 1134.
Ries, L., D. Melbert , et al. (2008). "SEER Cancer Statistics Review, 1975–2005." Retrieved June 13, 2008, from http://seer.cancer.gov/csr/1975_2005/
Ross, D., D. Siegel, et al. (1996). "Cell-specific activation and detoxification of benzene metabolites in mouse and human bone marrow: identification of target cells and a potential role for modulation of apoptosis in benzene toxicity." Environ Health Perspect **104**(**Suppl 6**): 1177–82.
Rundle, A., A. V. Roux, et al. (2007). "The urban built environment and obesity in New York City: a multilevel analysis." Am J Health Promot **21**(4 Suppl): 326–34.
Sakata, K., Y. Hoshiyama, et al. (2005). "Smoking, alcohol drinking and esophageal cancer: findings from the JACC Study." J Epidemiol **15**(**Suppl 2**): S212–19.
Samanic, C., W. H. Chow, et al. (2006). "Relation of body mass index to cancer risk in 362,552 Swedish men." Cancer Causes Control **17**(7): 901–19.
Sassi, F., H. S. Luft, et al. (2006). "Reducing racial/ethnic disparities in female breast cancer: screening rates and stage at diagnosis." Am J Public Health **96**(12): 2165–72.
Savitz, D. A. and K. W. Andrews (1997). "Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers." Am J Ind Med **31**(3): 287–95.
Schabath, M. B., M. R. Spitz, et al. (2002). "A myeloperoxidase polymorphism associated with reduced risk of lung cancer." Lung Cancer **37**(1): 35–40.
Schernhammer, E. S., F. Laden, et al. (2001). "Rotating night shifts and risk of breast cancer in women participating in the nurses' health study." J Natl Cancer Inst **93**(20): 1563–8.
Schlager, J. J. and G. Powis (1990). "Cytosolic NAD(P)H:(quinone-acceptor)oxidoreductase in human normal and tumor tissue: effects of cigarette smoking and alcohol." Int J Cancer **45**(3): 403–9.
Shen, H. M. and C. N. Ong (1996). "Mutations of the p53 tumor suppressor gene and ras oncogenes in aflatoxin hepatocarcinogenesis." Mutat Res **366**(1): 23–44.
Sillanpaa, P., L. Heikinheimo, et al. (2007). "CYP1A1 and CYP1B1 genetic polymorphisms, smoking and breast cancer risk in a Finnish Caucasian population." Breast Cancer Res Treat **104**(3): 287–97.
Silverman, D. T. (2001). "Risk factors for pancreatic cancer: a case-control study based on direct interviews." Teratog Carcinog Mutagen **21**(1): 7–25.
Silverman, D. T., R. N. Hoover, et al. (2003). "Why do Black Americans have a higher risk of pancreatic cancer than White Americans?" Epidemiology **14**(1): 45–54.
Silvestrini, R., E. Benini, et al. (1993). "p53 as an independent prognostic marker in lymph node-negative breast cancer patients." J Natl Cancer Inst **85**(12): 965–70.
Sinnett, D., M. Krajinovic, et al. (2000). "Genetic susceptibility to childhood acute lymphoblastic leukemia." Leuk Lymphoma **38**(5–6): 447–62.
Skibola, C. F., M. T. Smith, et al. (1999). "Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults." Proc Natl Acad Sci USA **96**(22): 12810–15.
Skibola, C. F., M. T. Smith, et al. (2002). "Polymorphisms in the thymidylate synthase and serine hydroxymethyltransferase genes and risk of adult acute lymphocytic leukemia." Blood **99**(10): 3786–91.
Smith, M. T., Y. Wang, et al. (2001). "Low NAD(P)H:quinone oxidoreductase 1 activity is associated with increased risk of acute leukemia in adults." Blood **97**(5): 1422–6.
Stanford, J. L., J. J. Just, et al. (1997). "Polymorphic repeats in the androgen receptor gene: molecular markers of prostate cancer risk." Cancer Res **57**(6): 1194–8.

Stern, M. C., K. D. Siegmund, et al. (2006). "XRCC1, XRCC3, and XPD polymorphisms as modifiers of the effect of smoking and alcohol on colorectal adenoma risk." Cancer Epidemiol Biomarkers Prev **15**(12): 2384–90.

Stolzenberg-Solomon, R. Z., B. I. Graubard, et al. (2005). "Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers." JAMA **294**(22): 2872–8.

Szilagyi, P. G., S. Schaffer, et al. (2002). "Reducing geographic, racial, and ethnic disparities in childhood immunization rates by using reminder/recall interventions in urban primary care practices." Pediatrics **110**(5): e58.

Taioli, E., S. Benhamou, et al. (2007). "Myeloperoxidase G-463A polymorphism and lung cancer: a HuGE genetic susceptibility to environmental carcinogens pooled analysis." Genet Med **9**(2): 67–73.

Taioli, E., J. Ford, et al. (1998). "Lung cancer risk and CYP1A1 genotype in African Americans." Carcinogenesis **19**(5): 813–17.

Taioli, E., L. Gaspari, et al. (2003). "Polymorphisms in CYP1A1, GSTM1, GSTT1 and lung cancer below the age of 45 years." Int J Epidemiol **32**(1): 60–3.

Taketa, K. (1990). "Alpha-fetoprotein: reevaluation in hepatology." Hepatology **12**(6): 1420–32.

Talcott, J. A., P. Spain, et al. (2007). "Hidden barriers between knowledge and behavior: the North Carolina prostate cancer screening and treatment experience." Cancer **109**(8): 1599–606.

Tanaka, F., Y. Shiratori, et al. (1996). "High incidence of ADH2*1/ALDH2*1 genes among Japanese alcohol dependents and patients with alcoholic liver disease." Hepatology **23**(2): 234–9.

Tanaka, F., Y. Shiratori, et al. (1997). "Polymorphism of alcohol-metabolizing genes affects drinking behavior and alcoholic liver disease in Japanese men." Alcohol Clin Exp Res **21**(4): 596–601.

Tang, D., J. J. Liu, et al. (2007). "Grilled meat consumption and PhIP-DNA adducts in prostate carcinogenesis." Cancer Epidemiol Biomarkers Prev **16**(4): 803–8.

Thomas, G., K. B. Jacobs, et al. (2008). "Multiple loci identified in a genome-wide association study of prostate cancer." Nat Genet **40**(3): 310–5.

Thompson, D., A. C. Antoniou, et al. (2005). "Two ATM variants and breast cancer risk." Hum Mutat **25**(6): 594–5.

Tiemersma, E. W., R. E. Omer, et al. (2001). "Role of genetic polymorphism of glutathione-S-transferase T1 and microsomal epoxide hydrolase in aflatoxin-associated hepatocellular carcinoma." Cancer Epidemiol Biomarkers Prev **10**(7): 785–91.

Toriola, A. T., S. Kurl, et al. (2008). "Alcohol consumption and risk of colorectal cancer: the Findrink study." Eur J Epidemiol **23**(6): 395–401.

Valverde, P., E. Healy, et al. (1996). "The Asp84Glu variant of the melanocortin 1 receptor (MC1R) is associated with melanoma." Hum Mol Genet **5**(10): 1663–6.

Verkasalo, P. K., J. Kaprio, et al. (1999). "Genetic predisposition, environment and cancer incidence: a nationwide twin study in Finland, 1976–1995." Int J Cancer **83**(6): 743–9.

Vineis, P. (2004). "Individual susceptibility to carcinogens." Oncogene **23**(38): 6477–83.

Vona-Davis, L., M. Howard-McNatt, et al. (2007). "Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer." Obes Rev **8**(5): 395–408.

Wenzlaff, A. S., M. L. Cote, et al. (2005). "GSTM1, GSTT1 and GSTP1 polymorphisms, environmental tobacco smoke exposure and risk of lung cancer among never smokers: a population-based study." Carcinogenesis **26**(2): 395–401.

Whitcomb, D. C., M. C. Gorry, et al. (1996). "Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene." Nat Genet **14**(2): 141–5.

Whittemore, A. S., L. N. Kolonel, et al. (1995). "Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada." J Natl Cancer Inst **87**(9): 652–61.

Wiencke, J. K., M. R. Spitz, et al. (1997). "Lung cancer in Mexican–Americans and African–Americans is associated with the wild-type genotype of the NAD(P)H:quinone oxidoreductase polymorphism." Cancer Epidemiol Biomarkers Prev **6**(2): 87–92.

Wikman, H., S. Thiel, et al. (2001). "Relevance of N-acetyltransferase 1 and 2 (NAT1, NAT2) genetic polymorphisms in non-small cell lung cancer susceptibility." Pharmacogenetics **11**(2): 157–68.

Wu, X., K. Gwyn, et al. (2001). "The association of microsomal epoxide hydrolase polymorphisms and lung cancer risk in African–Americans and Mexican–Americans." Carcinogenesis **22**(6): 923–8.

Xu, J., L. Dimitrov, et al. (2005). "A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics." Am J Hum Genet **77**(2): 219–29.

Yang, C. X., K. Matsuo, et al. (2005). "Esophageal cancer risk by ALDH2 and ADH2 polymorphisms and alcohol consumption: exploration of gene–environment and gene–gene interactions." Asian Pac J Cancer Prev **6**(3): 256–62.

Yu, M. W., C. I. Pai, et al. (2000). "Role of N-acetyltransferase polymorphisms in hepatitis B related hepatocellular carcinoma: impact of smoking on risk." Gut **47**(5): 703–9.

Zhang, S. M., I. M. Lee, et al. (2007). "Alcohol consumption and breast cancer risk in the Women's Health Study." Am J Epidemiol **165**(6): 667–76.

Zhang, Y., J. P. Wise, et al. (2004). "Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut Women." Am J Epidemiol **160**(12): 1177–83.

Zhou, W., G. Liu, et al. (2002). "Genetic polymorphisms in N-acetyltransferase-2 and microsomal epoxide hydrolase, cumulative cigarette smoking, and lung cancer." Cancer Epidemiol Biomarkers Prev **11**(1): 15–21.

Zhou, W., S. W. Thurston, et al. (2001). "The interaction between microsomal epoxide hydrolase polymorphisms and cumulative cigarette smoking in different histological subtypes of lung cancer." Cancer Epidemiol Biomarkers Prev **10**(5): 461–6.

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