Environmental and Occupational Causes of Cancer

A Review of Recent Scientific Literature

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TABLE OF CONTENTS

EXECUTIVE SUMMARY 1
INTRODUCTION 3
ESTIMATING ENVIRONMENTAL AND OCCUPATIONAL CONTRIBUTIONS TO CANCER 4
A Look at Recent History 4
Causes: Genes or Environment? 6
PERSPECTIVES ON RESEARCH METHODS 7
Epidemiologic and Animal Studies: Strengths and Limitations 7
Cancer Clusters 7
Cancer Incidence and Mortality Data 8
THE STATE OF THE SCIENCE 9
Methodology 9
The State of the Science by Cancer Type 12
Bladder Cancer 12
Bone Cancer 12
Brain and other Central Nervous System Cancers 12
Breast Cancer 13
Cervical Cancer 14
Colon Cancer 15
Esophageal Cancer 15
Hodgkin's Disease 15
Kidney Cancer 16
Laryngeal Cancer 16
Leukemia 17
Liver and Biliary Cancer 17
Lung Cancer 18
Mesothelioma 19
Multiple Myeloma 20
Nasal and Nasopharynx 20
Non-Hodgkin's Lymphoma 20
Ovarian Cancer 21
Pancreatic Cancer 21
Prostate Cancer 22
Rectal Cancer 22
Soft Tissue Sarcomas (STS) 23
Skin Cancer 23
Stomach Cancer 23
Testicular Cancer 24
Thyroid Cancer 24
COMMENTS AND DISCUSSION 25
RECOMMENDATIONS 29
REFERENCES 30
APPENDICES 37
Appendix 1. Substances and mixtures that have been evaluated by IARC as definite (group 1) human carcinogens and that are occupational exposures 37
Appendix 2. Occupations or industries evaluated by IARC as definitely, probably, or possibly entailing excess risk of cancer among workers. 39
Appendix 3. Definite or probable occupational carcinogens and carcinogenic circumstances, by site. 40
Appendix 4. Mortality rates from cancer and heart disease for ages younger than 85 and 85 and older,

1975-2001. 41
Appendix 5. Incidence rates for all cancer sites by race and sex for ages 64 and under, 1973-2001 42
Appendix 6. Incidence rates for all cancer sites by race and sex for ages 65 and over, 1973-2001. 43
Appendix 7. Mortality rates for all cancer sites by race and sex for ages 64 and under, 1969-2001 44
Appendix 8. Mortality rates for all cancer sites by race and sex for ages 65 and over, 1969-2001. 45
Appendix 9. Incidence rates for lung & bronchus cancers by race and sex, 1973-2001. 46

EXECUTIVE SUMMARY

Nearly one in two men and more than one in three women in the United States will be diagnosed with cancer at some point in his or her lifetime. Cancer is now the leading cause of death for individuals under age 85. Even though tobacco remains the single most significant preventable cause of cancer, it has been linked neither to the majority of cancers nor to many of the cancers that have increased rapidly in recent decades including melanoma, lymphomas, testicular, brain, and bone marrow cancers.

This paper summarizes recent scientific evidence of environmental and occupational links to nearly 30 types of cancer. It includes a critique of the 25 year-old analysis by Doll and Peto and subsequent analyses that attribute an extremely small fraction of cancer deaths to involuntary environmental and occupational exposures. The paper presents the state of the evidence on causal associations between environmental and occupational exposures and specific cancer types. The discussion of each cancer type is introduced by highlights of trends in incidence and mortality rates. Lastly, the paper considers additional indications that involuntary exposures are linked to cancers, such as patterns observed in different geographic areas and among different populations, including patterns of cancer in children.

The authors cite several notable findings:

- Cancer evolves from a complicated combination of multiple exposures. Attempting to assign certain exposures (i.e. diet, smoking, environment, etc.) certain roles in causing cancer that will total 100% is inappropriate given that no one exposure single-handedly produces cancer and many causes of cancer are still unknown. Comprehensive cancer prevention programs need to reduce exposures from all avoidable sources. Cancer prevention programs focused on tobacco use, diet, and other individual behaviors disregard the lessons of science.
- Examples of strong causal links between environmental and occupational exposures and cancer include:
  - Metals such as arsenic and cancers of the bladder, lung, and skin.
  - Chlorination byproducts such as trihalomethanes and bladder cancer.
  - Natural fibers such as asbestos and cancers of the larynx, lung, mesothelioma, and stomach.
  - Petrochemicals and combustion products, including motor vehicle exhaust and polycyclic aromatic hydrocarbons, and cancers of the bladder, lung, and skin.
  - Pesticide exposures and cancers of the brain, Wilms tumor, leukemia, and non-Hodgkin's lymphoma.
  - Reactive chemicals such as vinyl chloride and liver cancer and soft tissue sarcoma.
  - Metalworking fluids and mineral oils with cancers of the bladder, larynx, nasal passages, rectum, skin, and stomach.
  - Ionizing radiation and cancers of the bladder, bone, brain, breast, liver, lung, ovary, skin, and thyroid, as well as leukemia, multiple myeloma, and sarcomas.
  - Solvents such as benzene and leukemia and non-Hodgkin's lymphoma; tetrachloroethylene and bladder cancer; and trichloroethylene and Hodgkin's disease, leukemia, and kidney and liver cancers.
  - Environmental tobacco smoke and cancers of the breast and lung.

The sum of the evidence regarding environmental and occupational contributions to cancer justifies urgent acceleration of policy efforts to prevent carcinogenic exposures. By implementing precautionary policies, Europeans are creating a model that can be applied in the U.S. to protect public health and the environment. To ignore the scientific evidence is to knowingly permit tens of thousands of unnecessary illnesses and deaths each year.

INTRODUCTION

The purpose of this paper is to review scientific evidence, particularly epidemiologic evidence, regarding the contribution of environmental and occupational exposures to the overall cancer burden in the U.S. The discussion of this evidence has been an area of contention for at least the past three decades, since the assertion in 1977 by Higginson and Muir that 80% of all cancers were due to environmental exposures.[1] The evidence that Higginson and Muir invoked in their seminal article included, "descriptive epidemiological data relating to migrants, geographical variation in incidence, changes in risk over time, correlation studies, clusters and case reports." Although these authors were referring to "widespread general exposures of air and water pollution, the work environment, exposures resulting from personal choice such as smoking and drinking, and the diet," the concern that involuntary exposures to substances in the air, water, and work environment are major contributors to cancer in humans has persisted.

In the past three decades, there have been several efforts to estimate the proportion of cancer due to these involuntary exposures, starting with an ambitious effort by Doll and Peto and more recently by a group of authors at the Harvard Center for Cancer Prevention.[2, 3] In this paper, we review the evidence that Doll and Peto and other authors have summarized, and their resulting estimates of the proportion of cancer due to various factors. We also provide an alternative interpretation of the evidence and a caution against the very idea of attributing specific fractions or proportions of cancer to particular factors. In later sections, we review trends in cancer data and the state of the science regarding occupational and environmental exposures linked to various cancer sites. We conclude the paper by recommending that environmental and occupational links to cancer be given serious consideration by individuals and institutions concerned with cancer prevention, particularly those involved in research and public education.

ESTIMATING ENVIRONMENTAL AND OCCUPATIONAL CONTRIBUTIONS TO CANCER

A Look at Recent History

Over the past few decades, a number of researchers have attempted to estimate the proportion of cancer cases or deaths due to environmental and occupational exposures. Despite these well-intentioned efforts, it has only become more and more clear that cancers evolve through a complicated web of multiple causes and that it is not only pointless, but also counterproductive, to attempt to assign certain exposures a certain role in causing cancer. At the same time, scientific research has also made it clear that preventable environmental and occupational exposures are fueling excess cancer cases and deaths.

The 1981 Doll and Peto monograph was commissioned as a report to the Office of Technology Assessment of the U.S. Congress. It was published in the *Journal of the National Cancer Institute* and subsequently as a paperback book. These authors summarized the scientific literature in order to estimate the proportions of cancer deaths due to avoidable causes in the U.S., based on a complex series of arguments and interpretations of the epidemiologic data. They produced a summary table that estimated that 2% of cancer deaths were due to pollution and 4% to occupation, with ranges of acceptable estimates of less than 1% to 5% for the pollution contribution and 2 to 8% for the occupation contribution. In this same table, they estimate that the proportion of cancer deaths due to tobacco is 30% and to diet, 35%. A variety of other factors, including alcohol, food additives, reproduction and sexual behavior, industrial products, medicines, geophysical factors, and infection are ascribed percentages. The sum of the individual percentages is 97%, with a final category of "unknown" with no percentage. In this and a later paper, Doll and Peto acknowledge that some exposures interact with each other and that the true sum would have to be more than 100%, but this is impossible to estimate when all avoidable causes are still unknown.[4]

Although Doll and Peto clearly acknowledge that attributing causes of cancer to percentages that nicely add to 100% is an erroneous exercise, the field of cancer research has somehow missed this important point. It is difficult to estimate the impact of Doll and Peto's views, but their 1981 article had been cited in over 441 other scientific articles by the end of 2004. More importantly, it has been cited repeatedly by commentators who argue that "cleaning up the environment" is not going to make much difference in cancer rates.

In contrast, Landrigan and co-authors maintained that Doll and Peto's estimate of the contribution of cancer deaths due to occupation was too low and that it failed to take into account limitations on the data on which the estimate is based.[5] For example, Doll and Peto relied on epidemiologic studies of workers in large industries or broad categories of employment, but failed to consider exposures in smaller workplaces or from indirect contact with carcinogenic substances such as asbestos in maintenance operations. Landrigan, et al. and Davis, et al. also note that Doll and Peto limited their analyses to deaths in those under age 65 because they maintained that data on older decedents was unreliable. In doing this, they missed effects that are seen in older people whose cancers may have been caused by exposures while working. Landrigan and colleagues review other estimates of the proportion of cancer attributable to occupational exposures and settle on a central estimate of 10%, which they consider plausible based on their review of the literature and clinical experience.[6, 7]

In 1996, the Harvard Center for Cancer Prevention published a volume on causes of human cancer in which they updated Doll and Peto's estimates of avoidable causes.[3] This volume was produced with the purpose of providing context for the public, which "can become overly concerned about minimal risks while losing sight of major cancer risk factors that can be controlled or modified, in particular, tobacco use, diet, exercise and sun exposure." The short chapters on environmental pollution and occupation note 32 substances or industries judged to be carcinogenic to humans – Doll and Peto had listed only 16 in 1981 – but the summary table essentially duplicates the earlier estimate of the proportion of cancer deaths attributed to these two factors. In a summary section titled, "Public Concern about Environmental Carcinogens Is out of Proportion with the True Risk," the authors say:

> …with widespread news coverage of a variety of suspected carcinogens, public attention is drawn away from the most important causal

> factors – tobacco use, diet, obesity, and lack of exercise. Ironically, it is not uncommon to meet heavy smokers who are genuinely concerned about the possible health effects of magnetic fields, or 'environmental carcinogens' while denying or choosing to ignore the health impact of their smoking habit.

Today, most smokers are well aware of the health risks of smoking but are unable to overcome its addictive nature. More importantly, for decades, the tobacco industry unethically exposed both smokers and second-hand smokers to carcinogens without their knowledge.

The successive volumes of the Harvard Report have been widely cited and their arguments form the rationale for cancer control activities at many state and federal agencies, and appear to inform the approach of the American Cancer Society and other cancer organizations in the U.S. For example, a recent document released by the National Cancer Institute (NCI) and the National Institute for Environmental Health Sciences (NIEHS), called "Cancer and the Environment," notes that two-thirds of cancers are caused by environmental factors.[8] It reiterates the claim by Higginson twenty-five years earlier, and it defines environment as expansively as he did to include both voluntary and involuntary exposures. The NCI/NIEHS document describes the current understanding of the genetics and biology of cancer, including gene-environment interactions, the risk factors for various cancers, and then makes the following observation:

> At least two-thirds of the cases of cancer are caused by environmental factors. Many of these are linked to lifestyle factors that can be modified, such as cigarette smoking, excessive alcohol consumption, poor diet, physical inactivity, and being overweight and obese. For example, one-third of all the cancer deaths in this country could be prevented by eliminating the use of tobacco products. After tobacco, being overweight or obese appears to be the most important preventable cause of cancer. In addition to lifestyle choices, precautions can be taken in the home and workplace to reduce exposure to other harmful exposures.[8]

Although the title and tone of the NCI/NIEHS document sound different from the Harvard reports, the content is largely the same.

Another recent textbook which furthers these arguments is the *Textbook of Cancer Epidemiology*, co-edited by Adami, Trichopoulos, and Hunter, all of whom were major contributors to the Harvard Report on Cancer Prevention.[9] This encyclopedic work has chapters on, among other things, over twenty major cancer types. Each of these chapters reviews the major risk factors and practices or sources of carcinogenic exposures which increase risk. In most of these individual chapters there is a description of occupational contributions, although sometimes the discussion is basically to dismiss such contributions. For example, in discussing oral and pharyngeal cancer, the chapter authors say "occupational exposures do not contribute to a substantial proportion of total oral cancer cases." They do list several studies where excess oral cancer was found in rubber workers, cooks and others exposed to aromatic amines and phenoxy herbicides. In the chapter on bladder cancer, the chapter authors estimate that 4-10% of this type of cancer may be attributable to occupational exposures in such occupations at painter, machinist, mechanic, and workers in the metal, textiles, leather, shoemaking, hairdressing, dry cleaning, and transportation industries. They also cite specific chemicals such as benzidine, beta-naphthylamine, 4-aminobiphenyl, 5-o-toluidine, and polycyclic aromatic hydrocarbons as increasing bladder cancer risk.

The chapter on lymphomas in the *Textbook on Cancer Epidemiology* shows the tendency to dismiss the contribution of occupational and environmental exposures. Here, the authors list a fairly long series of studies of workers in various industries and those exposed to specific chemical compounds where excess risk of lymphoma was found. They end this discussion with a reference to a Centers for Disease Control and Prevention (CDC) study of exposure to the defoliant Agent Orange in Vietnam and make the claim that "the highest incidence of lymphoma was found in ground troops stationed in areas of lowest exposure and among sailors in navy ships off the coast of Vietnam." In contrast, the published articles they cite report that the highest risk of non-Hodgkin's lymphoma was in the veterans categorized as "Navy-shore," whose risk was 2.26, and in veterans who served in "I Corps," whose risk was 2.25 compared to controls. It is worth noting that Vietnam veterans diagnosed with lymphoma who served anywhere in Vietnam are now compensated by the Department of

Veterans Affairs for what is considered a service-related cancer.[10]

Causes: Genes or Environment?

Current knowledge of the mechanisms of cancer suggests that all cancers are both environmental and genetic, meaning that there are multiple causes that involve exposures originating outside the body as well as hereditary or genetic changes that converge to produce the disease. One recent description of this dynamic process reduces it to six essential alterations that may overwhelm the natural defenses built into human cells and tissues to produce a tumor.[11] The metaphor these authors use is an integrated electrical circuit, with multiple signaling pathways and feedback loops that can be altered or disrupted in various ways. Prevention of the alteration or disruption of cellular signaling and protective pathways can be accomplished by preventing carcinogenic exposures from outside the body from any source. Furthermore, these authors suggest that rational treatment of patients with cancer will follow from more detailed understanding of the particular alteration or disruption that has occurred. This is clearly still in the future for most types of cancer, so prevention of carcinogenic exposures is still the major priority.

Another line of research in the past few years has attempted to reveal gene-environment interactions whereby persons with particular genetic predispositions may be more susceptible to the effects of environmental exposures than others. Examples that are frequently cited are persons with BRCA1 or BRCA2 genes, alterations in the p53 gene that render those individuals less able to suppress the growth of cancer cells or alterations in the NAT gene that alter the ability to transform (or acetylate) environmental chemicals so that they produce cancer more readily. After several years of effort, it now appears that a very small percentage of individuals in any population have these genetic predispositions, but this cannot explain a large part of the excess cancer risk in studies of exposed groups.

In other words, the bulk of excess cancer in populations exposed to carcinogens is from the exposure itself, not from the excess risk in subgroups with a particular, rare, genetic predisposition.[12] Indeed in one occupational study of the aromatic amine, 2-naphthylamine, all 15 workers exposed to the distillation of the chemical in a small plant developed bladder cancer, thus demonstrating that individual susceptibility may be irrelevant in some situations (i.e. exposure to high levels of potent carcinogens).[13] Further research on more complex mechanisms, such as gene-gene-environment interactions and proteomics, is unlikely to change this conclusion, although these studies may deepen our understanding of the mechanisms by which cancers are produced.

Harri Vainio, currently head of the Finnish Institute for Occupational Health (and past head of Carcinogen Identification and Evaluation and later Chemoprevention for IARC), noted that it is likely that the attempt to use genetic markers "to identify susceptible sub-groups for public heath intervention would be too complex to be of practical value."[14] He also warned that over-emphasis on learning more about the mechanisms of gene-environment interactions carries the risk of ignoring opportunities for prevention that are right before us.

In theory, if a particular combination of exposures or interacting causes is required to produce a tumor in an individual, then prevention of any one of the components will prevent the tumor. A useful epidemiologic model for this is represented by a pie, which represents the sufficient cause of a specific disease in an individual.[15] The pie is made up of several component causes, or slices. Individual component causes alone are not sufficient to cause disease. Only when the whole pie of component causes is present, does sufficient cause for disease exist in that person. Different individuals may have different component causes comprising the complete or sufficient cause for their cancer, and for some cancers, a particular component may be present in many individuals with the disease. But it is impossible to estimate how these components add up to a specific proportion of the total cancer burden in the U.S. Furthermore, it is not necessary to propose a hierarchy or play one component cause off against another. Preventing carcinogenic exposures wherever possible should be the goal and comprehensive cancer prevention programs should aim to reduce exposures from all avoidable sources, including environmental and occupational sources.

PERSPECTIVES ON RESEARCH METHODS

Epidemiologic and Animal Studies: Strengths and Limitations

There are two major categories of research studies used to identify causes of cancer: animal and epidemiologic studies. Animal studies give the investigator the advantage of controlling the conditions under which animals are exposed at various levels to a given substance, their diet, and even their genetic make-up. Animal studies also allow the researcher to make conclusions about the likelihood that the tumor is caused by the exposure, since all other relevant factors are controlled. Human exposures, however, are not so easily controlled in either epidemiologic studies or case reports. In studies of individuals or groups of exposed people, there may be many unknown or uncontrolled factors that lead to difficulties in interpreting the results. People are continually exposed to multiple substances and these substances are likely to act synergistically at least some of the time. People also move from place to place and cancers often have a long latency period. In addition, many types of cancer are (or were) relatively rare, further complicating the ability of epidemiology to identify elevated rates.

The advantage of human studies, of course, is that they provide evidence of the effects in the species of greatest concern and do not require extrapolation from lab animals to humans. Epidemiologic studies are sometimes referred to as "natural experiments in the real world" that must be evaluated for potential sources of bias or chance that may have influenced the results.[16] When this evaluation is done by the authors of the study or by reviewers considering one study in the context of others on the same topic, it is possible to form an objective interpretation of the study's results. Epidemiology has established the necessary tools for controlling for potential sources of bias and for evaluating the potential role of chance. These tools allow us to draw well-founded, scientifically valid conclusions from epidemiologic studies.

Although there will be differences of opinion about the meaning or the weight to be given to epidemiologic studies, case reports, and animal studies, all agencies and organizations that classify human carcinogens consider this body of literature in some fashion. We undertake such a review in this paper, and, in so doing, we rely upon peer-reviewed, review articles by respected scientists primarily of epidemiologic studies.

Cancer Clusters

People occasionally perceive clusters of cancer in their communities or workplaces, and believe that they must have been caused by a common environmental exposure. These concerns are understandable and often lead to demands on local or state public health authorities to do some type of investigation or study to determine the cause. This is one of the most vexing issues facing public health because tools to investigate cancer clusters are crude and often inadequate. Furthermore, resources to do an unplanned investigation must be taken from other activities that may already be stretched thin. As a result, a typical public health response will be to explain away the apparent cluster as a statistical fluke, or an unfortunate play of chance. This rarely satisfies worried citizens or workers and leads to bad publicity and low levels of trust for public health authorities.

Our view is that cancer clusters can and do occur because of exposures from a common source. There are several famous examples of this including: the cluster of angiosarcoma of the liver in workers exposed to vinyl chloride at a manufacturing plant;[17] the cluster of clear-cell adenocarcinoma of the vagina in offspring of women who took DES;[18] and, the cluster of childhood leukemia in Woburn, MA residents exposed to contaminated drinking water.[19, 20] These examples give validity to concerns that exposures in other communities or workplaces might also generate legitimate cancer clusters, although it may be difficult or even impossible to determine this with presently available tools. History has shown that some clusters are indeed signals that a preventable exposure occurred, but we are aware that exposures linked to perceived clusters can be difficult to document. The proper response to such health concerns is not to dismiss them as improbable statistical artifacts, but to engage concerned families or workers and public health representatives in honest communication about what is known and what is not known about the exposures and the cancers that are perceived to constitute a cluster.

Many state public health agencies and non-governmental organizations have established protocols or guidelines for dealing with reported cancer clusters.[21] Typically, the steps involve investigating potential sources and routes of carcinogenic exposures, examining existing data from cancer registries, verifying reported cases, and then deciding whether to

do further statistical analyses or seek funds for a more detailed case-control study. These steps represent a rational approach, but the key ingredient, in our experience, is honesty and an open attitude and a willingness to listen carefully to people's concerns. As noted by Michael J. Thun and Thomas Sinks:

> While it is critical to triage reported clusters to determine which should be investigated more thoroughly, it is equally important to hear the community's concerns and provide information about how reports of cancer clusters are evaluated and what has been learned.[22]

Without this, there can be no satisfactory conclusion to a cancer cluster investigation, no matter how scientifically sound the steps appear on a flow chart.

Cancer Incidence and Mortality Data

Trends in cancer incidence and mortality are another important source of data for considering links between occupational and environmental exposures and cancers. These descriptive analyses by year, sex, race, age, and cancer type are invaluable tools for examining temporal changes in the patterns of cancer. Analyses of cancer incidence over time in specific populations are extremely useful for generating new hypotheses regarding possible risk factors for the disease. Because about half of newly diagnosed cancer cases do not result in death, mortality studies are more limited in their ability to indicate causes of cancer, but mortality data are crucial for understanding the burden of cancer in particular populations.

Heart disease was far and away the leading cause of death in the U.S. for all ages combined for nearly a century. In January 2005, the American Cancer Society (ACS) announced that beginning in 1999, cancer had surpassed heart disease as the leading cause of death for people under 85 (see Appendix 4). Cancer mortality for all sites declined somewhat in the 1990s, yet it has hovered around 200/100,000 for the past 60 years.[23, 24]

From 1950 to 2001, the incidence rate for cancer in all sites combined increased by 85%.[25] Between 1973 when NCI began its Surveillance, Epidemiology, and End Results (SEER) program and 1992, the incidence rate for all cancer sites rose by 32% from 385/100,000 to 510/100,000; it then declined to 477/100,000 in 2000 (see Appendices 5 & 6).[26]

Incidence rates for all cancer sites for those under 65 years of age steadily increased from 192/100,000 in 1973 to 229/100,000 in 1992 and stayed near that level through 2000. The much higher incidence rates for those 65 and over climbed even more significantly from 1,722/100,000 in 1973 to 2,452 in 1992 and then declined to 2,196 in 2000 (see Appendices 5 & 6).[26] The cancer mortality rate for those under 65 steadily declined from 86/100,000 in 1970 to 65 in 2001. However, cancer mortality for those 65 and over increased from 980 in 1970 to 1,162 in 1993 and then declined to 1,099 by 2001 (see Appendices 7 & 8).[27]

THE STATE OF THE SCIENCE

Methodology

In the following sections, we review the scientific literature (and reviews of the literature) on environmental and occupational exposures considered to cause cancer or suspected of causing cancer. To summarize the current scientific literature on causes of human cancer, we rely on a combination of reviews of epidemiologic studies of groups of individuals exposed at work or in their communities, and to a lesser extent, case reports of individual patients exposed to carcinogenic substances and experimental evidence from animal studies.

For each cancer type, we review the data trends as reported in NCI's Surveillance, Epidemiology, and End Results (SEER) Cancer Query Systems database, except as otherwise noted.[26, 27] All data are age-adjusted to the 2000 U.S. standard population. All rates are expressed as cases per 100,000 and reflect malignant cases only. All data exclude the most commonly diagnosed but rarely fatal cancers: non-melanoma skin cancers. SEER provides incidence data for the years 1973-2001[26] and mortality data for 1969-2001.[a 27] SEER provides racial information only for blacks and whites for these periods as a whole. For incidence data, we generally refer to the year 2000 for the most recent data because the year 2001 is somewhat more likely to be affected by late reporting. Where higher incidence rates were reported for 2001 than for 2000, we included data for 2001. According to a 2002 NCI study, the impact of late reporting on incidence data is considerable. In studying five cancer sites, Clegg et al. found that actual incidence rates were 3-14% higher than reported incidence rates. They also found that it takes 4-17 years for at least 99% of cancer cases to be reported.[28]

We present our summary by selected cancer sites and by major categories of exposure. Evidence from epidemiologic studies is the focus in this paper, given the importance it receives in considering causes of human cancer. We focus here on chemical and physical agents in the general environment and recommend that the reader seek other sources for information on tobacco (although we make some references to environmental tobacco smoke), diet (including alcohol), stress, reproductive factors, other lifestyle and behavioral factors, viral and bacterial exposures, and medical exposures and procedures. Similarly, we do not attempt to summarize the substantial body of literature addressing racial and socioeconomic disparities in cancer risk and differential exposures to occupational and environmental carcinogens. We recognize that there are several promising alternative ways of understanding the complex biology of cancer and that the emerging scientific literature on fetal and early life exposures may shed more light on the mechanisms of cancer in the future. We do not attempt to address the complexities of timing of exposure, dose, and additive or synergistic effects of multiple exposures, but a rapidly growing body of evidence points to their importance.[29, 15, 30]

We include highlights of recent trends in rates for the cancers we address for females and males and for blacks and whites in the U.S. (as explained above) and selected tables from Siemiatycki et al.,[31, 32] and graphs of selected cancer data trends. We recommend that our readers also refer to the informative database "Chemical Contaminants and Human Disease" prepared by Janssen, Solomon, and Schettler.[31]

Based on the Janssen, Solomon, and Schettler database,[31] we identified multiple categories of cancer types with the strongest scientific evidence of elevated risk due to environmental and occupational exposures. We searched MEDLINE articles using the keywords environment, occupation, chemicals, solvents, metals, radiation, etiology, and each of our selected cancer sites to access review articles from 1995 to 2004. In addition, we searched for reports of individual studies from 2002-2004. We also searched Google for organizations that publish peer-reviewed articles on the topic of environment and cancer.

Table 1 (below) briefly outlines the sources and uses of most of the carcinogenic agents reviewed. Please see Appendices 1-3 for additional information on substances and occupations classified as definite (group 1) carcinogens as causing cancer by the International Agency for Research on Cancer (IARC), occupational exposures to them, and the cancer sites with which they are associated.[32]

[a] This research was conducted prior to SEER's issue of data for 2002.

Table 1: Sources and Uses of Environmental and Occupational Carcinogens

Category	*Carcinogenic Agent*	*Source/Uses*
Aromatic Amines	Benzidine, 2-naphylamine, 4,4'-methylenebis 2-choloraniline (MOCA), chlornaphazine	Used as antioxidants in the production of rubber and cutting oils, as intermediates in azo dye manufacturing, and as pesticides. Common contaminant in chemical and mechanic industries and aluminum transformation and an air contaminant from tobacco smoking. Used widely in the textile and beautician (as hair dyes) industries.[13]
Chlorination Byproducts	Trihalomethanes	Trihalomethanes include chloroform, bromodichloromethane, chlorodibromomethane, and bromoform. Result from the interaction of chlorine with organic chemicals. Several halogenated compounds may form from these reactions although trihalomethanes are the most common. Brominated by-products are also formed from the reaction of chlorinated by-products with low levels of bromide in drinking water.[33]
Metals	Arsenic	Is produced commercially as a by-product of nonferrous metal production, primarily from copper production, comprising greater than 10% of dust content in some smelter operations.[34] Inorganic arsenic is primarily used to preserve wood, but is also used as a pesticide mainly on cotton plants. [35]
	Beryllium	Used in the nuclear, aircraft and medical devices industry. Used also as an alloy or in specialty ceramics for electrical and electronic applications. Found as a contaminant in the combustion of coal and fuel oil.[34]
	Cadmium	Occurs naturally in ores together with zinc, lead and copper. Used as stabilizers in PVC products, color pigment, several alloys and now most commonly in re-chargeable nickel-cadmium batteries. Also present as a pollutant in phosphate fertilizers.[36]
	Chromium	Chromium is used in steel and other alloy production. Chromium III and Chromium VI are used in chrome plating, the manufacture of dyes and pigments, leather tanning and wood preserving.[34]
	Lead	Used primarily in the production of batteries, ammunition, metal products such as solder and pipers and devices to shield X-rays. Lead is also found in gasoline, paints, ceramic products, caulking, and pipe solder, but has been reduced dramatically in the US.[37]
	Nickel	Used primarily as an alloy in stainless steel. Also used in nickel plating and battery production.[34]
Metalworking Fluids & Mineral Oils	Straight oils, soluble oils, synthetic and semi-synthetic fluids	Used in a variety of industries including metal machining, print press operating and cotton and jute spinning. [38]
Natural Fibers	Asbestos	An inorganic naturally occurring fibrous silicate particle used primarily in acoustical and thermal insulation. Asbestos fibers can be divided into two groups: chrysotile (most widely used) and amphibole which include amosite, crocidolite, anthophyllite, actinolite and tremolite fibers.[33]
	Silica	An inorganic particle used in foundries, brickmaking and sandblasting.[39]
Pesticides	Herbicides, Fungicides & Insecticides	Used for preventing, destroying, repelling or mitigating any pest or in use as a plant regulator, defoliant or desiccant.[40] The majority of pesticides as registered with the U.S. EPA are used in agricultural applications, although residential application is also an important source.[41]
Petrochemicals and Combustion Products	Petroleum products, motor vehicle exhaust (including diesel), polycyclic aromatic hydrocarbons (PAHs), soot, and dioxins	Petrochemicals are derived from natural gas or petroleum and used to produce a variety of other chemicals and materials including pesticides, plastics, medicines and dyes. Substances can be produced as the building blocks for other products, but mainly result from the incomplete combustion of burning coal, oil, gas (diesel exhaust), household waste, tobacco and other organic substances. Dioxins are a class of chemical that are the by-products of combustion processes containing chlorine and carbon-based chemicals such as polyvinyl chloride (PVC) plastics. Dioxins are also created during the chlorine-bleaching processes for whitening paper and wood pulp.[29]
Radiation	Ionizing radiation	Any one of several types of particles and rays given off by radioactive material, high-voltage equipment, nuclear reactions and stars. Alpha and beta particles, X-rays and gamma rays are radiation particles of concern to human health.[42]
	Non-ionizing radiation	Comprised of microwaves and electro-magnetic frequencies including radio waves and extremely low-frequency electric and magnetic fields. Cellular and mobile cordless telephones emit radiofrequencies in the microwave region of the electromagnetic spectrum. Radio frequencies at 300 MHz are created by radio, television, wireless telephony, emergency communications and radar among other sources. Extremely low frequency electromagnetic fields are emitted during the transmission and distribution of electrical power in the 60MHz region.[43]

Table 1: *Continued*

Category	*Carcinogenic Agent*	*Source/Uses*
Reactive Chemicals	Butadiene	Used in the production of polymers for the manufacture of styrene-butadiene rubber for tires, nitrile rubber for hoses, gaskets, adhesives and footwear; acrylonitrile-butadiene-styrene polymers for parts, pipes, and various appliances; and styrene-butadiene latexes for paints and carpet backing.[44]
	Ethylene oxide	Used as a sterilant, disinfectant and pesticide. It is also used as a raw ingredient in making resins, films and antifreeze.[44]
	Formaldehyde	Used primarily in the production of urea, phenol or melamine resins for molded products such a appliances, electric controls, and telephones; in particle-board and plywood and in surface coatings.[44]
	Mustard Gas	Produced and used primarily in World War I as a chemical warfare agent.[44]
	Sulfuric Acid	Used widely in industry for the production of isopropanol, ethanol; treatment of metals; and the manufacture of soaps, detergents and batteries.[44]
	Vinyl Chloride	Vinyl chloride is used in polyvinyl resins for the production of plastic pipes, floor coverings, and in electrical and transportation applications.[44]
Solvents	Benzene	Used as an intermediate in the production of plastics, resins and some synthetic and nylon fibers. Also used to make some types of rubbers, lubricants, dyes, detergents, drugs and pesticides. Is also found in crude oil, gasoline and cigarette smoke.[45]
	Carbon Tetrachloride	Used primarily in various industrial applications. Before being banned, was also used in the production of refrigeration fluid and propellants for aerosol cans, as a pesticide, as a cleaning fluid and degreasing agent, in fire extinguishers, and in spot removers.[46]
	Methylene Chloride	Used primarily as a solvent in a variety of industrial applications and as a paint strippers. It may also be found in some aerosol and pesticide products and in the production of photographic film.[47]
	Styrene	Used in the production of rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers and carpet backing.[48]
	Toluene	Used in the production of paints, paint thinners, fingernail polish, lacquers, adhesives and rubber. Also used in some printing and leather tanning processes.[49]
	Trichloroethylene (TCE)	Used mainly for degreasing metal parts. Previous used as a dry cleaning agent. TCE may be found in printing inks, varnishes, adhesives, paints and lacquers. Important contaminant in the general environment as a result of emissions & leakage from industrial settings.[50]
	Tetrachloroethylene (PCE)	Used to degrease metal parts and as a solvent in a variety of industrial applications. Since 1930s used by an increasingly large percentage of U.S. dry-cleaning operations.[51]
	Xylene(s)	Used as a cleaning agent, a thinner for paint and in paint and varnishes. Used in printing rubber and leather industries and found in small amounts in gasoline and airplane fuel. [52]
Other	Creosotes	Includes coal tar and coal tar pitch formed by high-temperature treatment of wood, coal or from the resin of the creosote bush. Wood creosote was historically used as a disinfectant, laxative and cough treatment. Coal tar products are used in medicine, animal and bird repellents and pesticides. Coal tar creosote is widely used as a wood preservative. Coal tar, coal tar pitch and coal tar pitch volatiles are used in roofing, road paving, aluminum smelting and coking.[53]
	Endocrine Disruptors	A number of chemicals capable of mimicking the body's natural hormones. See: http://www.ourstolenfuture.org/Basics/chemlist.htm
	Nitrates	Inorganic chemicals used heavily as agricultural fertilizers.
	Nitrosamines & N-nitroso compounds	A class of chemicals that forms as a result when amines and nitrosating agents chemically react and are found in the rubber, metal and pesticide industries, and in cosmetics and foods such as fried bacon and cured meets.
	Polychlorinated Biphenyls (PCBs)	Used as coolants and lubricants in transformers, capacitors and other electrical equipment. PCBs were banned in the U.S. in 1977.[54]

The State of the Science by Cancer Type

BLADDER CANCER

At 21.0/100,000, bladder cancer is the fifth most commonly diagnosed cancer for all population groups combined. Incidence rates increased somewhat from 18.1/100,000 in 1973 to 21.5 in 2000. White men have the highest rates at 42/100,000, followed by black men at 20/100,000. Rates increased and then declined over the past three decades, especially for blacks. White men also have the highest bladder cancer mortality rates (7.0) followed by black men (5.1). Overall, bladder cancer mortality has seen a gradual decline from 5.9 in 1970, the highest level recorded by SEER, to 4.3 in 2001.

The epidemiologic evidence linking ***metal*** exposure from arsenic with bladder cancer is strong and extensive.[55, 32, 33, 56] Much of the evidence comes from epidemiologic studies conducted in regions with high concentrations of inorganic arsenic contaminants in drinking water and in medicinal formulations such as Fowler's solution.[55] Several volatile chemicals have been linked with bladder cancer. Evidence from multiple studies examining ***chlorination by-products*** have consistently found elevated risk of bladder cancer, especially among populations with long-term exposure to chlorinated water.[55] One meta-analysis found that exposure to chlorinated surface water was associated with a statistically significant increase in the risk of bladder cancer.[57] Risk of bladder cancer from exposure to ***solvents*** is also suspected, particularly for the solvent tetrachloroethylene (PCE). In studies of dry cleaning workers, excess bladder cancer deaths have been found in well-designed cohort studies. Additional case-control studies have suggested a strong etiologic association between PCE exposure and bladder cancer mortality.[58]

Aromatic amines (arylamines) including 2-naphthylamine (ß-naphthylamine), benzidine, 4-aminobiphenyl, chlornaphazine (a derivative of 2-naphthylamine previously used in the treatment of polycythemia), as well as the manufacturing of auramine and magenta dye are well-established causes of bladder cancer, and one of the first carcinogens to be associated with an occupational exposure.[13, 32, 59] Studies of several other aromatic amines including O-toluidine and aniline have demonstrated elevated risks associated with bladder cancer.[13] Strong evidence demonstrates that workers in the rubber industry are at elevated risk for bladder cancer.[32, 60, 61] Elevated risk of bladder cancer has also been observed among occupations exposed to hair dyes.[62-64]

A number of epidemiologic studies have documented an increased risk of bladder cancer among workers exposed to ***petrochemicals and combustion products*** in different industries suggesting an association with polycyclic aromatic hydrocarbons (PAHs), to their nitroderivatives as well as diesel exhausts.[32, 65] An increase of bladder cancer risk, although inconsistent, is also found among industries with high exposure to PAHs from coal tars and pitches.[66] Studies of workers using ***metalworking fluids and mineral oils*** offer strong evidence for an association with bladder cancer.[32, 38, 63, 67] Recent reviews of studies of A-bomb survivors have documented elevated risks of bladder cancer associated with ***ionizing radiation***.[68] Other agents possibly associated with bladder cancer are seen in occupations entailing exposures to leather dusts, solvents other than tetrachloroethylene (PCE), paints and inks, as well as coal tar and pitches.[32, 65]

BONE CANCER

The incidence of bone and joint cancer increased from 0.7/100,000 in 1973 to 1.0 in the 1990s and then decreased to 0.8 in 2000. (For 2001, SEER reported the rate of 0.9.) Incidence rates are higher for whites and for men. At the same time, mortality due to bone and joint cancer decreased over the past three decades for all population groups from 1.0 in 1969 to 0.5 in 2001.

Exposure to ***ionizing radiation*** is a well recognized cause of bone cancer based on evidence from pioneering radiologists, radium dial painters atomic bomb survivors and patients treated medically with radiation.[32, 43] There is no safe dose of radiation and its damaging effects on genes are cumulative.[68] Its effects on cells may increase the ability of hormones or other chemicals to cause cancer. Radiation is a mutagen, carcinogen, and an initiator as well as a promoter of cancer. Exposures to radiation increased dramatically over the past 50 years with diagnostic x-rays, fluoroscopy, medical treatments, mammograms (which in their early years delivered high amounts of radiation), and CT scans.

BRAIN AND OTHER CENTRAL NERVOUS SYSTEM CANCERS

New cases of cancer of the brain and the central nervous system (CNS) increased from 5.3/100,000 in 1973 to 7.0 in 1990. By 2000, the rate of new diagnoses had declined to 6.7. Mortality rates

followed a similar pattern, rising from 4.0 in 1969 to 4.9 in the early 1990s. By 2001, the death rate had decreased to 4.4. Whites, particularly white men, have higher incidence and mortality rates than blacks overall.

Metals, primarily exposure to lead, have been weakly supported as risk factors of brain cancer by several studies including a meta-analysis of eight studies of populations with high occupational exposures to lead.[69-71] Additional studies provide limited evidence for increased risk of brain or CNS cancers and exposure to arsenic and mercury.[70, 72] Studies have suggested an association between exposure to ***solvents*** including benzene, toluene, xylene, and methylene chloride (particularly among women) and brain cancer.[70, 73] Studies of fathers occupationally exposed to solvents as well paints and/or inks provide limited evidence for increased risk of brain or CNS cancers among their children.[29, 59, 74]

Ionizing radiation is a proven etiologic agent associated with brain cancer based on evidence from therapeutic radiation studies and children exposed to diagnostic radiation in utero.[43, 59, 75] The evidence regarding risk of brain cancer from exposure to ***non-ionizing radiation*** from extremely low frequency electromagnetic fields is considered strongly suggestive based on studies examining both workers and children.[76] However, paternal exposure to electromagnetic fields associated with elevations of childhood nervous system cancers has also been suggested.[74] Studies are conflicting regarding the risk of brain cancer from exposure to microwaves and radio frequencies, primarily from cellular phone use, and exposure to radio and TV transmitters and are limited by poor detail on actual exposures and short follow-up periods.[77, 78]

Numerous studies have demonstrated that ***pesticide*** exposure is associated with CNS and brain cancer among children and adults.[32, 41, 70, 79, 80] Studies generally found greater risks among children associated with parental exposure to pesticides prior to conception and during pregnancy than for exposures experienced during childhood.[41, 80]

Multiple studies examining frequent maternal consumption of cured meats during pregnancy indicate that exposure to ***N-nitroso*** compounds increases the risk of CNS tumors in children.[59, 81] Scientists have found some evidence for increases of brain and CNS cancers among women in various industries including laboratories, rubber, painting, plastics, metals, wool and textile spinning, and petroleum refining.[72]

BREAST CANCER

Breast cancer is by far the most commonly diagnosed cancer for both black and white women. SEER estimated that nearly 2.3 million women were living with or had a history of breast cancer as of January 2002.[82] Breast cancer incidence rates increased by 43% from 99/100,000 in 1973 to 141/100,000 in 1998 and then decreased modestly to 135 by 2000. At 142 per 100,000 for white women in 2000, breast cancer approached three times the incidence rate for the second leading cancer diagnosis for white women – lung cancer. The breast cancer incidence rate for black women in 2000 was 116.

Breast cancer was the leading cause of cancer death for women of all ages combined until lung cancer surpassed it in 1988. It remains the leading cause of cancer death for women ages 25-54.[83] Breast cancer mortality for all groups increased from 31.8 in 1969 to 33.2 in 1989 and decreased to 26.6 in 2000.

Since SEER began tracking national cancer data in 1973, breast cancer incidence rates for women under 49 have been higher for blacks than for whites. By contrast, since 1981, black women of all ages have faced a higher risk of dying of breast cancer than white women. By 2001, breast cancer mortality for black women (34.5) was 33% higher than for white women (25.4).

The etiology of breast cancer may be among the most complicated of all cancers given inherent, life-long exposures to multiple endogenous and exogenous factors. Timing and dose are likely to have particular potency to the developing bodies of girls. The largest study ever conducted of twins (from Sweden, Denmark, and Finland) showed that non-shared environmental factors accounted for 67% of breast cancer risk, while inherited genes contributed 27%, and shared environmental factors 6%.[84]

Ionizing radiation is the best and longest established exogenous environmental cause of breast cancer.[84] More recent reviews of literature confirm elevated risks of breast cancer based on analyses of A-bomb survivors and medical radiation studies.[68]

Endocrine disruptors (also known as xeno-estrogens and synthetic estrogens) mimic the actions of estrogens and are found in many pesticides, fuels, plastics, detergents, and prescription drugs. In the early 1990s, Tufts University researchers discovered that p-nonyl-phenol (a common plastics additive) leaching from plastic tubing was causing breast cancer cells to grow. In 1994, Tufts researchers determined that certain pesticides are xenoestrogens because they promoted growth of breast cancer cells in culture.

Animal studies have linked bisphenol-A (BPA) to drastic changes in mammary gland development and polyvinyl chloride (PVC) to mammary gland tumors. [84] The general population is exposed to BPA in low levels via epoxy resins, polycarbonate plastic, and dental sealants.[85]

The tragic story of DES (diethylstilbestrol) has provided some of the most convincing evidence that synthetic chemicals can act like hormones. Daughters of women who took DES during pregnancy have more than twice the breast cancer risk of women in their age brackets who were not exposed to DES in utero.[84]

A number of ***solvents*** have been linked to increased breast cancer risk, particularly in occupational settings. Increased risks of breast cancer were shown in: 1) a Taiwanese study of electronics workers exposed to chlorinated organic solvents, 2) a government study of workers in a Scottish semiconductor plant, and 3) in a Danish study of women in solvent-using industries (fabricated metal, lumber, furniture, printing, chemical, textiles, and clothing industries).[84] A 1995 study suggested that occupational exposure to styrene and several organic solvents (including carbon tetrachloride and formaldehyde) was associated with increased risk. [86] A 1998 study of Shanghai Cancer Registry data found the highest increase in breast cancer risk among women in professional jobs, but the risk was also elevated for women exposed to organic solvents, benzene, and pesticides. [86] The Carolina Breast Cancer Study found a two-fold increase in breast cancer risk among women who did not wear protective gear while applying pesticides.[86]

California's Environmental Protection Agency categorized ***environmental tobacco smoke (ETS)*** as "causally associated" with breast cancer, especially among younger, premenopausal women. This 2005 meta-analysis of ETS studies determined that women of all ages exposed to ETS have a relative risk (RR) of 1.25 for breast cancer diagnosis, and when considering only studies with better exposure assessments, their RR was 1.91. Younger, primarily premenopausal women face a RR of 1.68 and when considering only studies with better exposure assessments, the RR for younger women was 2.20.[87]

A 1999 occupational study of women exposed to benzene and PAHs found the highest increase in breast cancer risk among those exposed to both substances.[86] In 2000, a British Columbia study found elevated breast cancer risk among women with occupational exposures to solvents and pesticides.[86] Certain solvents have been described as increasing cellular sensitivity to estrogens and progestins. Among these are ethylene glycol methyl ether (EGME) and its metabolite, 2-methoxyacetic acid (MAA).[84]

Researchers have established probable links, in some studies but not all, to breast cancer and ***pesticides*** including DDT/DDE, PCBs, hexachlorobenzene (HCB), hexachlorocyclohexane (lindane), heptachlor epoxide (a breakdown product of the insecticide heptachlor), and triazine herbicides (including atrazine). The body burden study conducted by the Copenhagen Center for Prospective Studies and the CDC showed that women with the highest levels of exposure to the pesticide dieldrin had twice the risk of developing breast cancer as women with the lowest levels. Women with higher levels of dieldrin also had higher breast cancer mortality.[84]

Probable links have with breast cancer have also been established for ***combustion by-products*** including PAHs and dioxin and ***reactive chemicals*** including ethylene oxide.[44, 88, 86] Additional possible links to breast cancer have been established for ***non-ionizing radiation*** from electromagnetic fields (EMFs), chemicals in sunscreens, phthalates (xenoestrogens in plastics), recombinant bovine somatotrophin (rBST), and zeranol (a nonsteroidal growth promoter with estrogenic activity).[84]

CERVICAL CANCER

The rate of diagnosis of new cervical cancer cases decreased from 17.2/100,000 in 1973 to 7.9 in 2001. During the 1970s and 1980s, rates for black women were double or more the rates for white women. While the incidence rate for black women remains higher than for white women, the rate for black women declined from 36.7/100,000 to 11.1/100,000 from 1973 to 2001. Likewise, mortality rates have declined, but have consistently been at least twice as high for black women as for white women. The cervical cancer mortality rate for black women dropped from 17.8/100,000 in 1969 to 4.8 in 2001. For white women, the rate dropped from 6.7 in 1969 to 2.4 in 2001.

Limited evidence links ***solvent*** exposure with cervical cancer. A comprehensive review of epidemiologic studies of exposure to trichloroethylene (TCE) yields evidence of increased risk of cervical cancer.[58] Studies of dry cleaning workers also demonstrate an increased risk of cervical cancer, suggesting a strong association with exposure to tetrachlorethylene (PCE), although workers were also exposed to other solvents and confounding by strong risk factor can not be

excluded.[32, 73] Evidence from one cohort study suggests an elevated risk of cervical cancer among workers exposed to non-specific solvents.[73]

COLON CANCER

Colon cancer incidence rates for all population groups increased from 39.9 per 100,000 in 1973 to 47.9 in 1985 and then decreased to 38.8 in 2000, slightly below the 1973 rate. In the 1970s, rates were higher for men and for whites, however, by the early 1980s, rates for blacks surpassed those of whites and were 30% higher by the year 2000 (whites = 38.5, blacks = 50.0). Mortality rates reflect the trends seen in incidence rates. Whites and men had the highest rates in 1969, yet, by 2001, the rates for black men and women were roughly 50% higher than those of their white counterparts. For all groups, mortality increased from 22.6 in 1969 to 23.7 in 1978 and then declined to 17.1 by 2001.

The evidence regarding environmental and occupational exposures related to the occurrence of colon cancer is generally limited and/or not consistent.[59] The evidence regarding risk to colon cancer from exposure to ***chlorination by-products*** is limited and conflicting.[55] Limited evidence from a few occupational studies suggest that colon cancer may be associated with exposure to the ***solvents*** xylene and toluene.[73] More recent studies of ***ionizing radiation*** suggest elevated risks associated with colon cancer.[68]

ESOPHAGEAL CANCER

New cases of esophageal cancer generally increased over the past three decades from 3.9/100,000 in 1973 to 4.9 in 1999. In 2000 and 2001, the incidence rate for all groups was 4.7/100,000. In 1978, when the incidence rate for black men was at its highest (24.4), it was six times greater than the rate for all groups combined (4.1). By 2001, the incidence rate for black males had declined to 11.1/100,000 – 2.4 times the rate for all groups combined. Mortality due to esophageal cancer increased from 3.5 in 1969 to 4.4 in 2001. Similar to the patterns of incidence, blacks, especially black men, face a much higher risk of dying of esophageal cancer than whites.

There is limited evidence for environmental determinants of esophageal cancer, partly due to its low incidence in the U.S. and other industrialized countries.[89] Suggestive evidence is offered for an increased risk of esophageal cancer associated with ***solvent*** exposure, notably PCE exposure.[32] Two large cohort mortality studies conducted by the NCI and the National Institute for Occupational Safety and Health (NIOSH) found that dry-cleaning and dye-house workers had twice the expected mortality rate for esophageal cancer. Even higher rates were found when analyzing only those workers exposed to PCE, those exposed for long durations, and latency of the disease.[51]

Interestingly, esophageal cancer is not found among laundry workers, a population similar to dry cleaners, but without the exposure to PCE.[58] Evidence from the most comprehensive cohort study and subsequent nested case-control study of workers exposed to ***metalworking fluids*** and ***mineral oils*** involved in grinding operations documented excess mortality from esophageal cancer.[38] Risk and mortality from esophageal cancer associated with exposure to ***combustion by-products*** such as soot is considered suggestive.[32]

HODGKIN'S DISEASE

The rate of diagnosis of new Hodgkin's disease cases decreased from 3.4/100,000 in 1973 to 2.8 in 2001. Mortality declined for all SEER population groups from 2.0 in 1969 to 0.5 in 2001. Whites and men are more affected by Hodgkin's disease than blacks and women in terms of incidence; however, mortality rates are about the same for white and black men. Hodgkin's disease incidence rates have been highest for those in their 20's, especially whites, since the 1970s. The overall rate for the 20-29 age group reached 6.1/100,000 in 1974 and again in 1988. In 2000, the incidence rate for this group was 5.0/100,000. For all adults, Hodgkin's disease incidence rates are lowest for those 40 and over. By contrast, mortality rates are highest for those 60 and older.

A number of case-control studies have indicated a risk of Hodgkin's disease following ***solvent*** exposure.[73] Although specific solvents have generally not been identified, a comprehensive review of epidemiologic studies of TCE offers some evidence of an association with Hodgkin's disease.[58] Excess risk has also been observed among laundry and dry cleaning workers, including one study of female workers.[58, 64] Some evidence supports an increased risk of Hodgkin's disease associated with benzene exposure.

Numerous descriptive and analytic studies examining workers exposed to ***pesticides*** have found elevated risk and mortality from Hodgkin's disease.[79] Studies examining exposure to specific pesticides including phenoxy acid herbicides and chlorophenols

provide some evidence of an association with Hodgkin's disease.[79, 90] In addition, limited evidence from a number of studies of occupational exposures to DDT suggests an association with Hodgkin's disease, although the findings may reflect combined exposure with other pesticides and chemicals.[91] Evidence from one large study of parental pesticide applicators and childhood cancer provides limited support for an increased risk of childhood Hodgkin's disease.[92]

Among other specific occupations, woodworking has consistently been linked with an increased risk of Hodgkin's disease.[93]

KIDNEY CANCER

The incidence of cancer of the kidney and renal pelvis steadily increased overall (and for each SEER population group individually) from 7.9/100,000 in 1973 to 12.3 in 2000. Rates are highest for blacks and for men. Kidney cancer mortality rates also increased steadily from 3.6 in 1969 to 4.3 in 2001. Both black and white men generally have twice the risk of their female counterparts of developing and dying from kidney cancer. In the late 1990s, mortality rates declined very slightly for women.

The effect of occupational and environmental exposures on kidney cancer is somewhat difficult because many studies only examine mortality, and kidney cancer is a disease of low mortality.[94] Even so, several agents emerge as risk factors for renal cancers. Kidney cancer has been linked to exposure to some ***metals*** including arsenic, cadmium, and lead. Although not considered conclusive, several studies of arsenic exposure in drinking water in regions of South America and Taiwan have documented excess mortality from kidney cancer.[55] Multiple studies have linked cadmium exposure to renal cancer, however, the evidence is not considered definitive based on null findings in more recent occupational studies.[36, 95, 96] Two recent studies and a meta-analysis examining kidney cancer in relation to lead exposure provide some evidence (albeit weak) of a causal link.[69]

Links have also been established with kidney cancer and ***solvent*** exposure. A thorough review of over 80 published papers and letters examining cancer epidemiology associated with exposure to trichloroethylene (TCE) found strong and consistent evidence of an increased risk of kidney cancer.[58] Some studies that assessed exposure using urinary biomarkers revealed compelling evidence for the association of kidney cancer and TCE. Whereas previous reviews of the literature concluded that TCE was at best weakly associated with kidney cancer, more recent well-designed cohort and case-control studies provide additional support, although the body of evidence is limited in its ability to isolate TCE from other solvent exposures such as PCE.[32, 51, 58] Multiple studies of laundry and dry cleaning workers provide evidence of elevated risk of kidney cancer associated with PCE exposure.[73] Increased kidney cancer rates have been observed among workers exposed to gasoline, particularly those who distribute gasoline.[61]

Several studies demonstrate an association with Wilm's tumor (a childhood cancer of the kidney) and exposure to ***pesticides***.[41, 80] Paternal employment as welder or mechanic has also been suggested as a risk factor for Wilm's tumor in children based on several studies.[81]

LARYNGEAL CANCER

In 1973, the incidence of cancer of the larynx was 5.1/100,000. It reached a high of 5.4 around 1980 and steadily declined to 4.0 by 2000. Men, particularly black men, are much more heavily affected by laryngeal cancer than women. The 2000 incidence rate was 11.3 for black men and 7.1 for white men. Overall, mortality declined from 1.7 in 1969 to 1.3 in 2001. The highest recorded mortality rate for white men was 3.4 in 1973. However, the highest mortality rates for black men (6.4) and black women (1.2) occurred in the early 1990s.

Evidence from studies of metal workers suggest a strong association with laryngeal cancer, especially among workers exposed to ***metalworking fluids*** and ***mineral oils***, (particularly straight oils).[38, 63, 67] The evidence is also considered strong for an increased risk of laryngeal cancer associated with ***natural fibers*** including asbestos exposure.[32] Consistent evidence from case-control studies, but not cohort studies, provides some evidence for an increased risk of laryngeal cancer among individuals exposed to wood dust.[61] Consistent evidence also supports an excess of laryngeal cancer among workers exposed to ***reactive chemicals*** such as sulfuric acids.[44]

Among other specific occupations, suggestive evidence is provided for excess risk of laryngeal cancer among rubber workers[32, 60] and strong evidence supports an association with the manufacturing of mustard gas, nickel refining, the "strong acid" process for the manufacturing of isopropyl alcohol, and diethyl sulfate in ethanol production.[32, 97]

LEUKEMIA

The rate of new diagnoses for leukemia has been relatively static for all population groups since SEER began keeping data. Incidence rates went from 12.5/100,000 in 1973 to a high of 13.3 several times from 1985-1995 and dropped slightly to 12.4 by 2000. Rates are highest for whites and for men. Leukemia mortality rates for whites gradually declined from 9.0 in 1969 to 7.8 in 2001. At the same time, leukemia death rates for blacks increased from 6.3 in 1969 to a high of 7.5 in 1996 and then declined to 6.7 by 2001.

Workers exposed to organic ***solvents*** have shown significantly elevated mortality from leukemia.[73] Based on a review of the epidemiologic evidence, scientific consensus concluded that benzene was etiologically related to the development of leukemia, specifically acute non-lymphocytic leukemia.[32, 73, 98] Subsequent evidence from a large-scale cohort study in China (a collaboration of the NCI and the Chinese Academy of Preventive Medicine) has emerged regarding the etiologic links between benzene and other leukemia subtypes (acute myelogenous, chronic myelogenous, acute lymphocytic, lymphocytic, and chronic lymphocytic) and risk of leukemias at low-levels of exposure.[98] Based on data from one occupational cohort, it has been estimated that a worker occupationally exposed to low benzene levels (average exposure of 1 ppm for 40 years) would nearly double his/her risk of dying from leukemia.[73]

Strong evidence demonstrates that employment in the rubber industry entails an elevated risk for leukemia, likely due to benzene and other solvents.[32, 60, 61] Evidence for an association between childhood leukemia and paternal exposure to solvents including benzene, carbon tetrachloride, and TCE as well as to paints and pigments is also quite strong.[74]

Exposure to ***reactive chemicals*** has shown elevated risk of leukemia. Limited evidence, primarily from one cohort study with a strong exposure assessment design provides support for elevated risk of leukemia among workers exposed to butadiene.[44] Limited evidence (primarily from one study) provides some support for an excess risk of leukemia associated with exposure to ethylene oxide.[44]

Exposure to ***ionizing radiation*** is a well-recognized cause of leukemia.[32, 42, 68] Prenatal exposure to from diagnostic radiography of mothers during pregnancy is an established cause of childhood leukemia.[99] One study of fathers occupationally exposed to ionizing radiation prior to conception was associated with increased risk of leukemia in their offspring, although these results have not been confirmed by subsequent studies.[99] The evidence is conflicting regarding the risk of leukemia from exposure to ***non-ionizing radiation*** including electromagnetic frequencies (EMFs).[77, 78, 100, 101] Although some informative studies have found elevated rates of leukemia associated with radio frequencies, methodological limitations including poor exposure assessments and short follow-up periods limit current evidence.[77, 100] However, on balance, a precautionary approach regarding exposure to EMFs is warranted, particularly for childhood leukemia.

Substantial evidence indicates that exposure to ***pesticides*** increases the risk of leukemia in both adults and children. Over a dozen studies found elevated rates of leukemia among children whose parents were occupationally exposed to pesticides or who used pesticides in their home or garden.[41] Increased risks of childhood leukemia have been documented as a result of parental exposures to pesticides prior to conception, in utero exposures, and direct exposures during childhood.[41, 80] One particular study suggests that insecticide exposure in utero places an individual at the highest risk for leukemia compared to exposures after birth.[102] Occupational studies of workers exposed to pesticides consistently demonstrate increased risk and mortality.[79] Exposure to specific pesticides including carbon disulfide, phosphine, and methyl bromide have been associated with excess mortality from leukemia.[79] In addition, evidence from a few studies of workers exposed to DDT provides limited support for an association with leukemia, notably chronic lymphatic leukemia.

Among other specific occupations, limited evidence supports an increased risk of leukemia among workers in the ***petroleum*** industry and workers exposed to ***ethylene oxide***.[32, 61, 103]

LIVER AND BILIARY CANCER

The incidence of liver and biliary cancer[b] in all population groups more than doubled from 2.7/100,000 in 1973 to 5.8 in 1999. By 2001, this rate had decreased slightly to 5.3 Rates for black men have generally been two or more times as high as the overall rate and this gap has only widened in recent years. In 2001, liver cancer incidence for black men was 13.5/100,000; for white men, it was 6.2; for black women, 3.2; and, for white women, 2.5. Mortality rates for liver cancer also increased over the past three decades, despite a downward trend in the 1970s. In 1969, mortality for all groups was 3.3/100,000. By

[b] SEER data are for liver and intrahepatic bile duct cancers, which exclude the gallbladder.

2001, it was 4.7. Mortality rates for men, especially black men, have consistently been higher than the rates for all groups combined. In 2001, liver cancer mortality for black men was 9.1/100,000; for white men 6.3; for black women 4.1; and, for white women 2.7.

Liver cancer has been linked with exposure to ***metals***, primarily arsenic.[32] Although not considered definitive, several studies suggest that ingesting arsenic in drinking water is associated with liver cancer.[33, 55]

Evidence from a meta-analysis of 55 cohort studies of mortality among workers exposed to organic ***solvents*** showed significantly elevated mortality from cancer of the liver and biliary tract.[73] Some studies have examined specific solvents. A comprehensive review of epidemiologic studies of trichloroethylene (TCE) exposure found a strong association with increased risk of liver and biliary cancers.[58] Other authors support these conclusions.[73] Although liver and biliary cancers are rare and some studies do not differentiate exposure to TCE from exposure to other solvents, incidence and mortality are elevated in the most compelling, well-designed cohort studies. Evidence for an increased risk of liver and biliary cancer associated with methylene chloride exposure comes from one cohort study of workers heavily exposed to methylene chloride in the production of cellulose triacetate fibers.[73]

Exposure to ***ionizing radiation*** is a well-established cause of liver cancer.[32, 68] Some evidence is offered for elevated risk of liver cancer associated with ***reactive chemicals***. Cohort studies consistently show an excess of liver cancer among vinyl chloride exposed populations and a meta-analysis of studies examining exposure to vinyl chloride found an elevated rate of mortality from liver cancer after excluding known deaths from angiosarcoma of the liver.[44, 104] An additional strong risk factor for liver cancer includes ***polychlorinated biphenyls*** (PCBs).[32]

LUNG CANCER

Lung cancer is the second most commonly diagnosed cancer, yet it is the number one cause of cancer death in the United States for men and for women. Overall incidence rates increased from 49/100,000 in 1973 to 70 in 1992 and then receded to 63 by 2000. Incidence rates are notably lower for women than for men, and they are much higher in black men than in white men (see Appendix 9). For women overall, lung cancer surpassed breast cancer as the leading cause of cancer death in 1988. Lung cancer death rates began to increase dramatically for men in the 1930s and for women in the 1960s. The overall death rate of 36/100,000 in 1969 rose to 59 in 1993 and declined to 55 by 2001. From the early 1970s to the mid-1990s, incidence and mortality rates for black men were more than double the overall rates.

Exposure to a number of ***metals*** has been linked to an increased risk of lung cancer. Strong evidence from multiple studies has demonstrated increased risk of mortality due to lung cancer from exposure to arsenic dusts resulting from mining and processing of arsenic-containing ore (lead, copper, and tin) as well as for individuals living near arsenic-producing industrial operations.[32, 34, 55, 59] Current studies are under investigation to determine whether particulates and sulfur dioxide released in the processing of arsenic-containing ore play a role in elevated mortality rates.[59] Increased risk of lung cancer has also been observed among workers involved in the manufacturing of arsenical pesticides.[34, 59] Studies of arsenic contamination in drinking water as a result of either natural or industrial contamination have consistently demonstrated increased risks for lung cancer.[33, 55, 104] Beryllium exposure among U.S. workers consistently shows excesses of lung cancer and is considered an established risk factor.[32, 34] Increases in exposure to cadmium and chromium (primarily hexavalent chromium salts) are also considered established risk factors for lung cancer based on evidence from occupational studies.[32, 34, 59, 95] Studies in workers show that some nickel compounds (sparingly soluble and soluble) are linked to lung cancer; however, these studies are limited because the workers had multiple exposures.[32, 34] Evidence from a meta-analysis examining the risk of lung cancer associated with lead exposure provides some support for a causal link, although studies on the issue may be confounded by concomitant exposure to arsenic.[69]

Exposure to a variety of ***solvents*** has also been linked to lung cancer. Based on evidence from a large Chinese cohort study, workers exposed to benzene had an excess risk of lung cancer.[73] Two well-conducted cohort studies have shown increased risks of lung cancer associated with exposure to toluene.[73]

Exposure to ***ionizing radiation*** is a well-recognized cause of lung cancer.[32, 42, 43, 68] In addition to studies of survivors of the atomic bomb, ionizing radiation exposure from radon has been consistently linked to lung carcinogenesis in eleven major epidemiologic studies of radon-exposed miners, primarily among uranium miners and more recently among hematite (iron-ore) and other metal-ore miners.[59, 105, 106] Findings of lung cancer deaths

associated with exposure to low levels of radon and improved understanding regarding the molecular basis of radon-induced tumors provides support for radon levels in the home environment and lung cancer, particularly among smokers.[105, 107] A recent combined analysis of seven case-control studies assessing residential radon exposure provides further evidence of elevated risk of lung cancer.[108]

Workers exposed to ***reactive chemicals*** have demonstrated elevations of lung cancer. Bis (chloromethyl) ether (BCME) and chloromethyl methyl ether (CMME), used primarily in the preparation of anion exchange resins, are established occupational carcinogens of the lung.[44] Exposure to mustard gas is also a well established lung carcinogen.[44] Suggestive evidence supports an excess of lung cancer among workers exposed to sulfuric acids.[32, 44]

Exposure to ***environmental tobacco smoke (ETS)***—a complex mixture of nearly 5,000 chemical compounds, 43 of which are known human or animal carcinogens—is an established cause of lung cancer based on numerous studies.[32, 66, 109, 110] Women who are life-long nonsmokers experience a 24% excess risk of lung cancer from exposure to spousal tobacco smoking.[111]

Studies of varied designs and diverse settings have repeatedly found rates of lung cancer associated with ***outdoor air pollution***, mainly from exposure to fossil fuel.[112, 113] Although a meta-analysis of numerous case-control and cohort studies is not possible because of heterogeneity in study designs, on the whole, the studies tend to show an increased risk of lung cancer among the highest-exposed workers, which do not seem to be attributable to confounding factors such as smoking or occupational exposure.[33] However, some researchers argue that the strength of the evidence for the risk of lung cancer and air pollution is considered modest due to inconsistencies between studies and a limited ability to demonstrate dose-response effects.[114] Although examination of carcinogenic risks from individual chemicals in air pollution is difficult, there is a biological rationale for links to cancer from numerous compounds including benzo[a]pyrene, benzene, some metals, particles, and possibly ozone.[33] Studies in regions of China and other countries of ***indoor air pollution*** from combustion sources used for heating and cooking, as well as high levels of cooking oil vapors, have identified these exposures as risk factors for lung cancer.[33]

Substantial evidence from multiple studies examining both occupational and residential exposure ***to petrochemicals and combustion by-products*** provides support for an association with lung cancer. Exposure to PAHs has been repeatedly shown to increase lung cancer risk.[32, 66] Evidence from two meta-analyses of workers exposed to diesel exhaust provides strong evidence for elevated risks of lung cancer.[59] Suggestive evidence supports a causal link between lung cancer and exposure to coal tar and pitches and strong evidence supports a link to soot.[32] Evidence from populations most highly exposed to dioxin provides some support for an increased risk of lung cancer.[32, 115]

Elevations of lung cancer have been observed in occupational studies examining exposure to ***pesticides***, notably DDT, although these findings are somewhat inconsistent.[79, 116] A more recent large cohort study of pesticide applicators provides some evidence for increased risk of lung cancer associated with the insecticides chlorpyrifos and diazinon and the herbicides metolachlor and pendimethalin.[117] Several studies of printing workers exposed to ***metalworking fluids*** based on mineral oil formulations have found excess lung cancer, although these excesses have not been observed in other industries such metal machinists with similar exposures.[32, 38] Strong evidence supports an increased risk of lung cancer associated with exposure to ***natural fibers*** including silica, wood dusts, asbestos (all fiber types), and other mineral fibers although evidence is conflicting for man-made fibers such as glass wool, rock/slag wool, and ceramic fibers.[32, 39, 118] Some evidence supports an excess risk of lung cancer in other specific industries, including the rubber industry.[60, 63]

MESOTHELIOMA

Mesothelioma incidence rates rose from 0.5/100,000 in 1973 to 1.2 in the early to mid-1990s and then receded to 1.1 in 2000. Rates for white men are highest – they more than tripled from 0.8 in 1973 to 2.7 in 1992 and dropped back to 2.3 by 2000. Rates for black men were higher than the overall rate from the late 1980s to the late 1990s, but were below the rates for all groups combined in 2000 and 2001. SEER does not provide mortality data for mesothelioma, but the National Institute for Occupational Safety and Health included a 1999 mortality rate in *WoRLD report 2002*.[119] The overall mortality rate was 0.012/100,000 and rates for men were much higher than for women. The death rate for white men was 0.024 and for black men 0.010. Health, United States, 2003 provides numbers of deaths for selected years. It

reported 531 in 1980, 725 in 1990, and 2,384 in 2000 and 2,429 in 2002.[83] [c]

The ***natural fiber,*** asbestos (all fiber types) exposure is an established cause of mesothelioma of the pleura and peritoneum.[32, 39]

MULTIPLE MYELOMA

The incidence of multiple myeloma increased from 4.6/100,000 in 1973 to a peak of 6/100,000 in the 1990s and decreased to 5.3 in 2001. Black men have the highest rates of myeloma – their incidence rate was 16.1 in 1973 and 13.0 in 2001. The 2001 rates were next highest for black women (9.3), followed by white men (6.1) and white women (4.1). Mortality rates due to myeloma increased from 2.5 in 1969 to 4.0 in the early 1990s and receded to 3.8 for 1998-2001. Incidence rates are highest for blacks and secondarily for white men. In 2001, the black male mortality rate was 8.7 and for black females, it was 6.3.

Solvent and ***ionizing radiation*** exposure has been linked to increased risk of multiple myeloma. Despite the common use of 1,1,1-trichloroethane as a metal cleaning solvent, there are limited studies on cancer risk; two of which have found an increased risk of multiple myeloma based on small numbers.[73] Some studies have linked multiple myeloma with benzene exposure.[98, 103] Exposure to various ***pesticides*** including those contaminated with dioxin has been associated with multiple myeloma in some studies.[120] A review of epidemiologic studies of personal and occupational exposure to hair dyes suggests an elevated risk of multiple myeloma.[62, 64]

NASAL AND NASOPHARYNX

The numbers of cases of nasopharynx cancer[d] are small enough that the data are somewhat unstable. Overall, incidence rates fluctuated between 0.6 and 0.8/100,000 from 1973 to 2001. Rates have generally been highest for blacks and for men. Rates for black men have usually been at least double the rates for white men and women combined. For all groups, mortality rates declined from 0.3/100,000 in 1969 to 0.2 in 2001. Again, rates are highest for men and for blacks. A black man has four times the risk of dying of nasopharynx cancer as a white woman.

Studies of occupational exposure to ***metals*** have documented increased risks of nasal and nasopharynx cancers. Epidemiologic studies of workers engaged in chromium chemical production and use provide suggestive evidence that chromium is an strong risk factor for nasal cancers.[32, 34] They also show that some nickel compounds (sparingly soluble and soluble) are also strong risk factors for nasal cancers.[32, 34]

Based on a large Chinese cohort of workers exposed to the ***solvent*** benzene, there is some evidence of an increased risk of nasopharynx cancer.[73] Some ***reactive chemicals*** have been associated with nasopharyngeal and nasal cancers including limited evidence supporting excess risks associated with exposure to formaldehyde.[32, 44] Workers exposed to ***metal-working fluids*** such as mineral oil as well as ***natural fibers*** such as wood dust have also consistently demonstrated elevated risks of nasal cancer.[32, 63] ***Ionizing radiation*** exposure has also been linked to nasal cancers based on evidence from radium dial painters.[121] Among other specific occupations, strong evidence from studies in England and Italy supports an increased risk of nasal cancer among workers in the boot and shoe industries.[61]

NON-HODGKIN'S LYMPHOMA

The incidence of non-Hodgkin's lymphoma (NHL) doubled from 10/100,000 in 1973 to 20/100,000 in 1997. Except for black women, the rate of new diagnoses declined slightly by 2001; however, incidence and mortality rates are highest among men and whites. Mortality rates for NHL steadily increased from 5.6/100,000 in 1969 to 8.9/100,000 in 1997 and then declined to 7.9 by 2001.

Numerous case-control studies have reported an increased risk of NHL following occupational exposure to organic ***solvents.***[73] Several case-control studies have suggested a relationship between benzene and NHL with 3-fold increases among one group of workers and risks rising to 4-fold among workers with ten or more years of benzene exposure.[98, 122] Benzene is also suspected in association with increases in NHL observed among children living near railways, oil refineries, and petrochemical plants.[122] There is also support for increased risk of NHL following exposure to trichloroethylene (TCE), tetrachloroethylene (PCE), and styrene.[32, 58, 73]

Although the evidence is somewhat conflicting, multiple studies have documented elevated risks of NHL among agricultural and forestry workers exposed to ***pesticides.***[79] Of studies that have examined specific pesticides, increased risk and death from NHL have been associated (though not definitively linked) with phenoxy acid herbicides, chlorophenols and or-

[c] Note that ICD-9 used the term "cancer of the pleura," which may not always be considered mesothelioma.

[d] SEER tracks cancers of the nasopharynx and does not provide data on nasal cancers.

ganophosphorous insecticides, carbon disulfide, phosphine, methyl bromide, and ethylene dibromide.[79, 90] Several investigators have suggested that the phenoxy acid herbicide 2-4 D has been associated with 50-200% excess of NHL although a recent review of the evidence for 2-4 D disagrees with these findings.[90, 123] Limited evidence from a number of studies of occupational exposures to DDT and a case-control study examining adipose tissue levels of other organochlorine pesticides (i.e. dieldrin, oxychlordane, heptachlor) provides some support for increased risks of NHL.[91] Evidence from a few studies provides limited support for an increased risk of childhood lymphoma (including both Hodgkin's disease and NHL) associated with parental occupational exposure to pesticides.[92]

Substantial evidence links NHL with dioxin exposure, although not all studies are in agreement.[32, 115, 122, 124, 125] Several studies have linked higher chlorinated congeners of PCBs in adipose tissue with NHL, consistent with findings that PCBs are immunotoxic substances.[122] A review of the epidemiologic evidence regarding occupational and personal exposure to hair dyes suggests that hair dye exposure can produce a small elevation in NHL risk.[62, 123] The highest risks for NHL and hair dye use have been associated with dark hair dyes.[123] Additionally, use of hair dyes before 1980 (prior to widespread reformulation of all oxidative dye products) showed a 30% increase in NHL.[123]

OVARIAN CANCER

The incidence rate of ovarian cancer for all women declined from 16.5/100,000 in 1973 to 13.9 in 2001. Rates were consistently higher for whites than for blacks throughout this period. Mortality rates also declined gradually over the last three decades, from 10.4 in 1969 to 9.0 in 2001. White women have approximately a 50% greater risk of developing ovarian cancer than black women and a 25% greater risk of dying of ovarian cancer.

Scientific research consistently demonstrates an association between women working in graphics and printing industries and increased risks of ovarian cancer.[126] Although the causal agent has not been identified, the printing industry uses several possible carcinogens including solvents, mineral oils, oil mists, PAHs, and printing inks and pigments to name a few. Limited evidence exists linking ovarian cancer with ***pesticides***, primarily from women reporting personal use of the herbicide atrazine.[79] Recent studies of ***ionizing radiation*** exposure also suggest elevated risks for ovarian cancer.[68]

Although numerous studies have linked perineal use of talc powder with ovarian cancer, some studies have found conflicting results.[127] Based on a meta-analysis of exposure to talc powder comprising 16 studies, researchers found a statistically significant increased risk of ovarian cancer associated with talc exposure, although the evidence was limited by the lack of a clear dose-response relationship.[127]

Among other specific occupations, limited evidence supports an excess of ovarian cancer risk among hairdressers and beauticians.[126]

PANCREATIC CANCER

Incidence rates for pancreatic cancer rose and fell modestly over the past three decades, ending at 11.2/100,000 in 2000, somewhat below their 1973 level of 12.3. Both incidence and mortality rates are higher for blacks and for men. Overall, mortality rates dropped slightly from 11.1/100,000 in 1969 to 10.5/100,000 in 2001, but rates for both black and white women were slightly higher at the end of this period than at the beginning.

Some evidence is provided linking elevated rates of pancreatic cancer with exposure to ***metals*** including cadmium and nickel.[128] ***Solvent*** exposure has been linked with pancreatic cancer. Studies of dry cleaning and laundry workers provide some evidence for an increased risk of pancreatic cancer.[51, 58, 73] However, a lack of more defined exposure assessments in these studies limits drawing conclusions about an etiologic association with a specific solvent.[58] Evidence from two cohort studies of workers heavily exposed to methylene chloride suggests an excess risk of pancreatic cancer.[73]

Reactive chemicals have also been associated with pancreatic cancer. A meta-analysis of formaldehyde exposure and pancreatic cancer provide weak evidence for an association due to the fact that increases were only found in some occupations, but not others having the highest exposure to formaldehyde.[129] Strong evidence also supports an increased risk of pancreatic exposure associated with exposure to acrylamide.[32]

Limited support is offered for an association of pancreatic cancer and ***pesticides***. Evidence from a nested case-control study of chemical manufacturing workers with long-term exposure to DDT and DDT derivatives suggest a causal link to pancreatic cancer.[91] Studies of metal workers involved in grinding operations offer substantial evidence for an association with exposure to ***metalworking fluids and mineral oils*** or other cutting oils.[38, 63]

PROSTATE CANCER

Prostate cancer is by far the most commonly diagnosed cancer in men and is the second leading cause of cancer death in men. Prostate cancer incidence for all men combined nearly tripled from 85/100,000 in 1973 to the PSA test-induced spike of 237/100,000 in 1992. By 2000, the rate had decreased to 179. Prostate cancer afflicts black men far more than white men. The 2000 incidence rate was 174 for whites and 283 for blacks. Mortality rates increased significantly from 1969 to the early 1990s, especially for black men, and have decreased over the past decade. While prostate cancer incidence rates were 63% higher for black men than for white men in 2000, mortality rates were 2.5 times higher for black men (68.7) than for white men (27.7) in 2000.

Demonstrated environmental risk factors for prostate cancer include dietary fat, particularly from animal fat and red meat, cadmium, and pesticides.[85] Some ***pesticides,*** notably herbicides and other ***endocrine disruptors***, are likely to be associated with elevated risks. Excess risks have also been found for exposure to ***metallic dusts*** and ***metalworking fluids***, ***PAHs***,[e] and liquid fuel ***combustion products***, among other substances.[130, 131]

Studies of the extreme geographic variations in prostate cancer incidence around the globe (up to 30-fold) and changes in incidence or mortality among migrants from developing to developed countries provide the strongest evidence that diet and/or environmental factors play a significant role in prostate cancer etiology.[132, 133] Cooking red meat produces various ***aromatic amines***, many of which have proven to be carcinogens in animal studies. PhIP[f] is one of the aromatic amines and it is known to cause invasive prostate cancer in rats. Consumption of red meat or other animal fats may prompt undetectable, low-grade prostate tumors to grow into more aggressive cancers.[85]

Metals including cadmium and arsenic have been linked to prostate cancer. Although multiple studies have linked prostate cancer among individuals both occupationally and environmentally exposed to cadmium, the evidence is not considered definitive.[34, 36, 95] However, recent in vitro experiments indicate that human prostate epithelial cells can be a target of the oncogenic effect of cadmium.[95] A few studies of arsenic in drinking water suggest an association with prostate cancer, although the data are too limited to be considered conclusive.[55]

Studies also suggest increased risk of prostate cancer associated with ***pesticide*** exposures.[79] A number of occupational studies, though not all, have shown an elevated risk of prostate cancer incidence and/or mortality among farmers and pesticide applicators. The findings of elevated risk for the latter group are particularly significant. One in vitro study showed that several organochlorine pesticides, a pyrethroid, and a fungicide separately caused proliferation of androgen-dependent human prostate cancer cells.[85] One possible explanation for variable findings pertains to the wide variety of pesticides and herbicides.

Considerable evidence associates exposure to endocrine disrupting chemicals in the environment with prostate cancer and suggests that the timing of the exposure is critical, especially in the cases of fetuses and developing boys. In 1980, a report showed that in utero exposure to DES correlated with enlarged prostatic ducts and an increase in the Leydig cells in the testes.[85] BPA has been shown to cause enlargement of the prostate in mice exposed in utero to low levels.[85]

RECTAL CANCER

Incidence rates for rectal cancer[g] declined for all groups from 17.9 in 1973 to 14.7 in 2000. In 1973, the risk of developing rectal cancer was 80% higher for white men than for black men. By 2001, this gap had more or less vanished – the rate for white men was 18.5 and for black men, 18.9. The 2001 incidence rate for black women was 12.3 and for white women, 10.4. In 1969, the rectal cancer mortality rate was 6.8 overall, with white men having the highest rate (9.1). By 2001, the mortality rate for all groups had dropped to 3.0, but black men had the highest risk of dying of rectal cancer (4.5).

Exposure to ***solvents*** has been linked to rectal cancer. Several studies suggest an increased risk of rectal cancer associated with exposure to toluene and xylene.[73] There is also evidence to suggest an association between rectal cancer and ***chlorination by-products*** in drinking water.[55, 57] However, based on a meta-analysis that demonstrated statistically significant increased risks of rectal cancer and conflicting findings in two of the most recent case-control studies, an expert

[e] Those exposed to PAHs include firefighters, power plant operators, foundry workers, coke oven workers, furnace, kiln, and oven operators, chimney sweeps, railway workers, heavy equipment operators, farm machine operators, and paving and stone cutting workers (Parent & Siemiatycki 2001).

[f] 2-amino-1-methyl-6-phenylimidazol[4,5-*b*]pyridine.

[g] The SEER rates addressed here are for cancers of the "rectum and rectosigmoid junction."

working group on the issue stated that the evidence for rectal cancer and chlorination by-products was inconclusive.[57] Substantial evidence from studies among workers exposed to ***metalworking fluids*** and ***mineral oils*** demonstrates an increased risk for rectal cancers, particularly among workers involved in grinding operations.[38, 63, 67]

SOFT TISSUE SARCOMAS (STS)

The incidence rate of soft tissue sarcomas (STS) (including heart) increased from 2.3/100,000 in 1973 to 3.0 in 2001. Incidence rates are highest for men, especially black men. Mortality due to soft tissue sarcomas also increased – from 0.9/100,000 in 1969 to 1.5 in the mid-1990s and then decreased to 1.3 in 1999-2001. Mortality rates have tended to be highest for black men and women, followed by white men.

Evidence supporting a link with soft tissue sarcomas and ***metals*** is provided only among some studies suggesting elevated rates of STS among patients treated with arsenical medications. The ***reactive chemical*** vinyl chloride monomer is an established cause of angiosarcoma of the liver.[32, 104] Based on a meta-analysis of studies examining cancer mortality associated with exposure to vinyl chloride, elevations of STS were observed, although the authors cautioned that the results may have been influenced by an under diagnosis of true angiosarcoma.[104] Angiosarcoma of the liver is also suggested to be associated with exposure to arsenic based on some occupational studies. Exposure to ***ionizing radiation***, which is received by radium workers and patients receiving medical treatment, is a highly recognized cause of both bone and sinus sarcomas but is less strongly recognized in association with STS.[42, 81, 134]

Risk of STS has repeatedly been elevated in studies examining exposure to ***pesticides*** among farmers, forestry and horticulture workers, and pesticide applicators.[79] Ewings sarcoma studies examining exposure to phenoxy acid herbicides, chlorophenols with and without contamination with dioxins, and DDT offer suggestive evidence for an increased risk of STS.[79, 91]

Strong evidence supports excess rates of STS associated with exposure to dioxin.[32, 115, 124, 125] Limited evidence from one case-control study suggests that fluoridated water could be linked with osteosarcoma.[135]

SKIN CANCER

Non-melanoma skin cancers (namely basal and squamous cell) are by far the most commonly diagnosed cancers, though they are rarely fatal. More than 1 million new cases are expected this year.[136] Melanoma of the skin is relatively rare among blacks, but among whites, the incidence rate tripled from 7.5/100,000 in 1973 to 22.6 in 2001. Mortality due to melanoma also increased steadily during this period for whites from 2.1/100,000 in 1969 to 3.0 in 2001.

Ionizing radiation is a well recognized cause of non-melanoma skin cancer based on evidence from studies of atomic bomb survivors and radiologists.[42, 43, 68] Exposure to ultraviolet radiation and sun exposure is a definitive cause of all types of skin cancer including melanoma.[32, 43]

Metals such as inorganic arsenic are well recognized as skin carcinogens. A review of dozens of epidemiologic studies of arsenic contamination in drinking water (either as a product of natural or industrial contamination), found consistent associations between high levels of arsenic exposure and non-melanoma skin cancer.[33, 55] Studies examining medicinal uses of arsenic such as Fowler's solution (potassium arsenic), also demonstrated skin carcinogenicity.[34, 55] There is established evidence that early formulations of ***metalworking fluids*** and ***mineral oils*** used in cotton and jute spinning and metal machining were carcinogenic to the skin and an established cause of scrotal cancer among workers in the textile and metalworking industries.[38, 63, 137]

Exposure to creosotes used as wood preservatives is an established cause of non-melanoma skin cancer in addition to exposure to PAHs and coal tars.[32, 66 32, 79] Percival Pott first linked scrotal cancer to an occupational exposure in 1775 when he noticed an elevated incidence among small boys who assisted chimney sweeps. This association was later attributed to PAH exposure.[138, 139, 140, 141, 142] In the 1950s, researchers identified an increased incidence of scrotal cancer among men working with cutting oils.

Among other specific occupations, limited evidence supports an increased risk of skin cancer, particularly melanoma, among workers in the petroleum industry.[61]

STOMACH CANCER

Overall, new diagnoses of stomach cancer declined steadily from 13.1/100,000 in 1973 to 8.1 in 2001. Incidence and mortality rates are twice as high for blacks as for whites and twice as high for men as for

women. For all of SEER's population groups, mortality rates declined from 10.7 in 1969 to 4.3 in 2001.

Evidence from multiple cohort and case-control studies suggests that exposure to ***metals*** such as lead is associated with stomach cancer.[69] Studies in China among populations exposed to high levels of nitrates in drinking water suggest links between nitrate contamination and stomach cancer.[55] Although a study in France failed to demonstrate such an association, evidence from the China studies (which also linked histology patterns of gastric lesions with nitrate levels and found that cancer rates increased with the in vitro mutagenicity of drinking water) provides sufficient evidence to warrant further study.[135]

Stomach cancer has been associated with ***ionizing radiation*** based on studies of atomic bomb survivors, radium dial painters, and radiologists.[143, 68] There is some evidence of risk of stomach cancer associated with ***solvent*** exposure, primarily to toluene, based on a number of studies of workers in a number of different industries.[73] Elevated risks of stomach cancer have been observed in occupational studies examining exposure to ***pesticides*** although the findings are inconsistent.[79] Strong evidence from multiple studies of occupations with exposure to ***metalworking fluids*** and ***mineral oils*** supports an increased risk of stomach cancer, with the highest risk observed among workers involved in grinding operations.[38, 67] Strong evidence supports an association of stomach cancer and high levels of ***asbestos*** exposure.[143] Excess risk of stomach cancer has also been found in workers in rubber, coal, iron, lead, zinc, and gold mining industries. One study of the rubber industry suggested that stomach cancer may be associated specifically with workers exposed to particulates generated during the mixing of dry ingredient and to fumes and reaction products emitted during milling. [60, 61, 143]

TESTICULAR CANCER

The incidence of testicular cancer generally increased over the past three decades from 3.3/100,000 to 5.7 in 2000. Incidence rates in 2000 were several times higher for white men (6.7) than for black men (1.6). Death rates for testicular cancer, on the other hand, saw a steady decline for both whites and blacks from 0.9 in the early 1970s to 0.2 in 2001. Mortality is higher for white men, but survival rates are lower for black men.

Male reproductive development disorders (including testicular cancer) are widely considered to be related to exposure to ***endocrine disrupting*** chemicals particularly in utero. Indeed some environmental chemicals have been observed to alter endogenous levels of androgens (certain phthalates) and estrogens (PCBs and polyhalogenated hydrocarbons).[144] In utero exposure to DES is strongly suspected to increase the exposure of male fetuses to xenoestrogens. Tests on mice have linked increased risk of testicular neoplasia and testicular cancer with in utero exposure to DES.[145]

In one case-control study, mothers of men with testicular cancer had significantly elevated concentrations (2-4 times as high as mothers of controls) of the sum of the 38 tested polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), *trans*- and *cis*-nonachlordane, and the sum of tested chlordanes.[146] A literature review of testicular cancer found significantly elevated risks of testicular cancer in men working in specific industries including agriculture, tanning, and mechanical industries and consistent associations with painting, mining, plastics, metal working, and occupational use of hand-held radar.[147] However, some of the studies examined had a small number of exposed subjects and may have yielded "spurious" results requiring further analysis.[147]

Ganmaa et al. theorized that changing patterns in testicular cancer in Japan following World War II were due to changes in diet, namely to increased consumption of milk and dairy products. They hypothesized that estrogens and saturated fats in dairy products might explain the increase in testicular cancer.[148]

THYROID CANCER

The incidence of thyroid cancer increased from 4.2/100,000 in 1973 to 8.0 in 2001. Rates are highest for white women, followed by black women, and lowest for black men. The rate of new diagnoses in white women increased from 5.6 to 12.4 in 2001. Mortality, by contrast, decreased slightly from a high of 0.7 in 1970 to 0.5 in 2001. Black women had the highest mortality rates through this period – 0.8 in 1969 and 0.6 in 2001.

Survivors of the atomic bomb, patients treated medically with radiation, workers at nuclear facilities and residents exposed to radioactive fall-out are all part of the body of evidence definitively linking exposure to ***ionizing radiation*** as a cause of thyroid cancer.[32, 42, 43, 149, 68] Recent evidence from studies of the Chernobyl accident demonstrates strong concern for increased risk of thyroid cancer among exposed children.[149]

COMMENTS AND DISCUSSION

The scientific literature provides substantial evidence of environmental and occupational causes of cancer and fully justifies accelerated efforts to prevent carcinogenic exposures. In fact, to ignore the scientific evidence is to knowingly permit thousands of unnecessary illnesses and deaths every year. In addition to all of the evidence cited above under "The State of the Science," we find many other indications that environmental and occupational exposures are linked to cancers.

The single greatest risk factor for cancer is age – and our population is aging. But cancer rates are age-adjusted. If we look only at incidence patterns among those aged 65 and over or 85 and over, we still find a significant increase over the past three decades. The same holds true when we look at what has happened with children – and when we look at what has happened to Americans from 20 to 64 years of age.[26] It's not that more of us are old or that more of us live long enough to get cancer.

Cancer became a widespread disease – of epidemic proportions in certain cancer sites – within a single generation. But our genes simply don't change that fast. In approximately 1950, about one in four Americans could expect a cancer diagnosis at some point during his or her lifetimes. Today, nearly one in two men and more than one in three women can someday expect to hear, "you have cancer."[136, 150] Cancer is now the second-leading cause of death overall, and the first leading cause of death for Americans under the age of 85 (see Appendix 4).[136]

Incidence rates for some cancer sites have increased particularly rapidly over the past half century. From 1950-2001, melanoma of the skin increased by 690%, female lung & bronchial cancer increased by 685%, prostate cancer by 286%, myeloma by 273%, thyroid cancer by 258%, non-Hodgkin's lymphoma by 249%, liver and intrahepatic duct cancer by 234%, male lung & bronchial cancer by 204%, kidney and renal pelvis cancers by 182%, testicular cancer by 143%, brain and other nervous system cancers by 136%, bladder cancer by 97%, female breast cancer by 90%, and cancer in all sites by 86%.[25]

Looking at a more recent window, the list of cancers fastest on the rise changes. From 1992-2001, liver cancer increased by 39%, thyroid cancer increased by 36%, melanoma increased by 26%, soft tissue sarcomas (including heart) by 15%, kidney and renal pelvis cancers by 12%, and testicular cancer increased by 4%.[151]

Nearly twenty years ago, the U.S. EPA projected that tens of thousands of additional skin cancer fatalities would result from what was then a 5% loss of the ozone layer above North America. Melanoma affects our protective skin barrier, while non-Hodgkin's lymphoma affects the lymph nodes, which are designed to protect our bodies from outside invaders. Lymphomas appear to have a consistent association with synthetic chemical exposures, particularly with exposure to a class of pesticides introduced in 1942 and known as phenoxy herbicides. They include the defoliant Agent Orange, which is considered responsible for the excess cases of non-Hodgkin's lymphoma among Vietnam veterans.[10] Myeloma is associated with exposure to ionizing radiation, solvents used in the rubber and painting industries, other industrial solvents, metals, and petroleum.[152]

Even though tobacco smoke remains the single most significant preventable cause of cancer, it has been linked neither to the majority of cancers nor to many of the cancers that have increased rapidly in recent decades including melanoma, lymphomas, testicular, brain, and bone marrow cancers. Testicular cancer most commonly affects men in their 20s and 30s. Incidence rates for testicular cancer in this age group increased by at least 75% from the 1970s to the 1980s and remain around 11 to 13 per 100,000. This increase cannot be attributed to improved diagnosis.[136, 26] Between 1973 and 1992, brain and other nervous system cancers increased by 32% among all population groups from 5.3 to 7.0/100,000 and then dropped back modestly to 6.7 in 2000. Those aged 65 and older, however, experienced a 109% increase in brain and CNS cancers from 10.0 in 1973 to 20.9 in 1992 and their rates have remained at this elevated level.[26, 153]

The rise and fall of lung cancer has tracked the rise and fall of the prevalence of smoking, with expected, distinct time delays for men and for women. Stomach cancer incidence dropped dramatically over the past century – probably due to the development of better food handling and higher consumption of fresh foods as refrigeration eliminated food preservation methods that were more toxic like salting, smoking, and

pickling.[152] Better control of *H. Pylori* infections also played a role in reducing stomach cancer.[154]

If ethnicity were to play a significant role in determining cancer risk, then immigrants should retain the cancer incidence rates of their country of origin. Yet, immigrants to a new land acquire the cancer rates of their new home within one to two generations.[155, 156, 157, 158, 159]

Elevated cancer rates follow additional patterns – the disease is more common in cities, in farming states, near hazardous waste sites, downwind of certain industrial activities, and around certain drinking-water wells. Patterns of elevated cancer incidence and mortality have been linked to areas of pesticide use, toxic work exposures, hazardous waste incinerators, and other sources of pollution.[152, 160, 161, 162, 59]

The U.S. EPA's long-delayed and highly politicized "Draft Dioxin Reassessment" released in 2000 admitted that the weight of the evidence from epidemiologic studies suggested that, "the generally increased risk of overall cancer is more likely than not due to exposure to TCDD [dioxin] and its congeners." The report went on to conclude, "The consistency of this finding in the four major cohort studies and the Seveso victims is corroborated by animal studies that show TCDD to be a multisite, multisex, and multispecies carcinogen with a mechanistic basis."[163]

Farmers in industrialized nations die more often than the rest of us from multiple myeloma, melanoma, prostate cancer, Hodgkin's lymphoma, leukemia, and cancers of the lip and stomach. They have higher rates of non-Hodgkin's lymphoma and brain cancer. Migrant farmers experience elevated rates of multiple myeloma as well as cancers of the stomach, prostate, and testis.[152]

The National Cancer Advisory Board reported to Congress in 1994 that inadequate acceptance of the importance of contaminants in food and the environment had been an obstacle in cancer prevention. People may choose their diets, but they neither choose nor usually know about environmental carcinogens that may be present in food and water.[152]

The growing burden of cancer on children may provide some of the most convincing evidence of the role of environmental and occupational exposures in causing cancers. Children do not smoke, drink alcohol, or have stressful jobs. In proportion to their body weight, however, "children drink 2.5 times more water, eat 3 to 4 times more food, and breathe 2 times more air" than adults.[152] In addition, their developing bodies may well be affected by parental exposures prior to conception, exposures in utero, and the contents of breast milk. We have learned how to save more lives, thankfully, but more children are still diagnosed with cancer every year. The incidence of cancer in all sites combined among children ages 0-19 increased by 22% from 13.8/100,000 in 1973 to 16.8 in 2000 and most of this increase occurred in the 1970s and 1980s.[26, 152, 153]

Epidemiologic studies have consistently linked higher risks of childhood leukemia and childhood brain and central nervous system cancers with parental and childhood exposure to particular toxic chemicals including solvents, pesticides, petrochemicals, and certain industrial by-products (namely dioxins and polycyclic aromatic hydrocarbons).[29]

A considerable portion of the evidence presented above in "The State of the Science" derives from occupational studies, in part because the workplace can provide the structure that epidemiologic studies need. Unequal workplace exposures among different populations provide further indications of the ability of occupational exposures to cause harm. The long-term mortality study of steelworkers found the highest lung cancer mortality (SMR = 10.8) among non-white workers who spent more than five years working on top of the oven. The same study found that of the few white workers in this occupational category, a negligible portion died of lung cancer.[164] Long-term benzene workers have a relative risk of dying of leukemia of more than 30. More than half of asbestos workers have died of cancer and the relative risk of lung cancer among asbestos workers who smoke is 55.[6]

The fact that men develop and die from cancer more often than women is another clue to the importance of occupational exposures over lifestyle choices. Occupationally linked cancer deaths in the 1990s were likely to reflect exposures from the 1950s to 1970s, when sex differences were more marked in the workplace. At the same time, elevated rates of bladder and salivary gland cancers have been identified among women in traditionally female occupations such as hair dresser.[152]

From 1972 through 2003, the International Agency for Research on Cancer (IARC) evaluated over 880 substances, complex mixtures, and industrial process. IARC classified 89 of these substances as definite human carcinogens, 64 as probable human carcinogens, and 264 as possible human carcinogens. Siemiatycki et al. determined that these groupings consisted of 28 definite, 27 probable, and 113 possible human *occupational* carcinogens. Siemiatycki et al. then identified 18 occupations or industries that have been consi-

dered by IARC to definitely, probably, or possibly entail "excess risk of cancer among workers" (see Appendix 2). Siemiatycki and colleagues also summarized the substantial cumulative evidence that occupational exposures cause many types of cancer (see Appendix 3).[32]

Many Americans are exposed to multiple sources of carcinogens on a daily basis – regardless of where they work. In 1991, the National Research Council estimated that one in every six Americans lived within four miles of a Superfund site. According to the U.S. EPA's website, "the chemicals found at Superfund sites range from familiar contaminants, like arsenic, lead, mercury, and DDT to less familiar chemicals such as toluene, trichloroethylene, and pentachlorophenol."[165] Most of the 1,241 sites on today's National Priorities List did not exist prior to World War II.[166] Most plastics, detergents, solvents, and pesticides and the by-products of their manufacture came into being after World War II. From the late 1950s to the late 1990s, we disposed of more than 750 million tons of toxic chemical wastes.[152]

Since the U.S. EPA began its Toxic Release Inventory (TRI) program in 1987, total releases have declined, however, in 2002, the most recent year reported, 24,379 facilities in the U.S. reported disposing of or otherwise releasing 4.79 billion pounds of over 650 different chemicals. (TRI data do not include toxic vehicle emissions, the majority of releases of pesticides, volatile organic compounds, and fertilizers, or releases from numerous other non-industrial sources.)[167] In 2001, more than 1.2 billion pounds of pesticides were used in the United States and over 5.0 billion pounds in the world as a whole.[150]

When Rachel Carson published her landmark book, *Silent Spring*, in 1962, she sounded alarm bells about the implications of the massive increase in U.S. production of synthetic pesticides from 124 million pounds in 1947 to 638 million pounds in 1960: "We have subjected enormous numbers of people to contact with these poisons, without their consent and often without their knowledge."[168] She added:

> What sets the new synthetic insecticides apart is their enormous biological potency….they destroy the very enzymes whose function is to protect the body from harm, they block the oxidation processes from which the body receives its energy, they prevent the normal functioning of various organs, and they may initiate in certain cells the slow and irreversible change that leads to malignancy.[168]

Carson described as "ironic" the prospect that we might alter our own fate by the seemingly "trivial" choice of an insect spray:

> Future historians may well be amazed by our distorted sense of proportion. How could intelligent beings seek to control a few unwanted species by a method that contaminated the entire environment and brought the threat of disease and death even to their own kind? Yet this is precisely what we have done.[168]

Several studies have found links between childhood cancer and exposure to pesticides. Most of the studies linked pesticide exposure with an increased likelihood of childhood leukemia, brain cancer, NHL, soft tissue sarcoma, and non-Hodgkin's lymphoma, although the studies varied on the magnitude of the impact.[29]

More than 25 years ago, under the Carter Administration, an Interagency Regulatory Liaison Group, directed by Eula Bingham of the Occupational Health and Safety Administration (OSHA), produced a report entitled, "Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks." They concluded that because of the variable susceptibility of individuals and their unknown, life-long, background exposures to carcinogens: "Even if thresholds for carcinogens could be demonstrated for certain individuals or for a defined population, no reliable method is known for establishing a threshold that could apply to the total human population."[169]

The day before Carter left office, Bingham issued a proposed rule (which became known as the "generic carcinogens policy") that would have, among other things, taken into consideration when classifying substances as carcinogens, "whether the molecular structure of the substance is similar to the molecular structure of another substance which meets the definition of a potential occupational carcinogen;…"[170] Two months later, the Reagan administration nullified the rule.[171]

The magnitude of the problem we face and the urgency of acting upon what we know can be traced back to the 1940s. In 1948, Wilhelm Heuper, a prescient senior NCI scientist, wrote:

> Environmental carcinogenesis is the newest and one of the most ominous of the end-products of our industrial environment. Though its full scope and extent are still unknown, because it is so new and because the facts are so extremely difficult to obtain, enough is known to make it obvious that extrinsic carcinogens present a very immediate and pressing problem in public and individual health.[172]

In 1964, Wilhelm Hueper and his NCI colleague, W. C. Conway, described patterns in cancer incidence as "an epidemic in slow motion":

> Through a continued, unrestrained, needless, avoidable and, in part reckless increasing contamination of the human environment with chemical and physical carcinogens and with chemicals supporting and potentiating their action, the stage is being set indeed for a future occurrence of an acute, catastrophic epidemic, which once present cannot effectively be checked for several decades with the means available nor can its course appreciably be altered once it has been set in motion.[173]

RECOMMENDATIONS

In this paper, we have briefly summarized the state of the epidemiologic science on the most compelling environmental and occupational links to multiple cancer sites. This paper cannot do justice to the full body of knowledge, nor to understandings of the subtleties of timing and dose, nor to the complicated synergistic interactions between more than one environmental exposure and between genes and environmental exposures. Further research is needed, but we will never be able to study and draw conclusions about the potential interactions of exposure to every possible combination of the nearly 100,000 synthetic chemicals in use today. Despite the small increased risk of developing cancer following a single exposure to an environmental carcinogen, the number of cancer cases that might be caused by environmental carcinogens is likely quite large due to the ubiquity of carcinogens. Thus, the need to limit exposures to environmental and occupational carcinogens is urgent.[33]

A main concern for Sandra Steingraber, author of *Living Downstream: An Ecologist Looks at Cancer and the Environment*, is not whether the greatest dangers are presented by dump sites, workplace exposures, drinking water, food, or air emissions:

> I am more concerned that the uncertainty over details is being used to call into doubt the fact that profound connections do exist between human health and the environment. I am more concerned that uncertainty is too often parlayed into an excuse to do nothing until more research can be conducted.[152]

Certainly, more research is called for – and it should be funded by those who produce or emit synthetic chemicals. We need a more detailed review of the state of the science. We also need a companion paper to this one addressing the state of toxicological science on environmental and occupational links to cancers.

At the same time, uncertainty and controversy are permanent players in scientific research. However, they must not deter us from enacting regulations and policies based on what we know and pursuing the wisdom of the precautionary principle. This is not new thinking, as demonstrated by Sir Austin Bradford Hill's 1965 address to the Royal Society of Medicine:

> All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone action that it appears to demand at a given time.[174]

The least toxic alternatives should always be used. Partial, but reliable, evidence of harm should compel us to act on the side of caution to prevent needless sickness and death. The right of people to know what they are being exposed to must be protected.

We would not be charting new territory. The European Union is using the precautionary principle to implement a comprehensive policy on chemicals regulation: Registration, Evaluation and Authorization of Chemicals (REACH). This policy aims to protect public health and promote a non-toxic environment, while preventing ill effects on the European market and enhancing innovation and competitiveness of European industry. Among its specific objectives are: requiring that industry be responsible for generating information on chemicals, for evaluating risks, and for assuring safety; extending responsibility for testing and management to the entire manufacturing chain; using safer substitutes for chemicals of high concern; and, encouraging innovation in safer substitutes.[175] The United States has much to learn from the REACH approach.[h]

In the words of ecologist Sandra Steingraber: "It is time to start pursuing alternative paths. From the right to know and the duty to inquire flows the obligation to act."[152]

[h] Please see www.chemicalspolicy.org and http://www.panda.org/campaign/detox/index.cfm for more information on this and other chemical policy initiatives in the European Union.

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APPENDICES

Appendix 1. Substances and mixtures that have been evaluated by IARC as definite (group 1) human carcinogens and that are occupational exposures

Source: Siemiatycki et al. Listing occupational carcinogens. *Environmental Health Perspectives.* 112(15):1447-57, Nov 2004.

Table 3. Substances and mixtures that have been evaluated by IARC as definite (group 1) human carcinogens and that are occupational exposures.

Substance or mixture	Occupation or industry in which the substance is found[a]	*IARC Monograph* volume (year)[b]	Human evidence[c]	Animal evidence[c]	Site(s)
Physical agents					
Ionizing radiation and sources thereof, including, notably, X rays, γ rays, neutrons, and radon gas	Radiologists; technologists; nuclear workers; radium-dial painters; underground miners; plutonium workers; cleanup workers following nuclear accidents; aircraft crew	Vol. 75 (2000a) Vol. 78 (2001a)	Sufficient	Sufficient	Bone[d] Leukemia[d] Lung[d] Liver[d] Thyroid[d] Others[d]
Solar radiation	Outdoor workers	Vol. 55 (1992b)	Sufficient	Sufficient	Melanoma[d] Skin[d]
Respirable dusts and fibers					
Asbestos	Mining and milling; by-product manufacture; insulating; shipyard workers; sheet-metal workers; asbestos cement industry	Suppl. 7 (1987)	Sufficient	Sufficient	Lung[d] Mesothelioma[d] Larynx[e] GI tract[e]
Erionite	Waste treatment; sewage; agricultural waste; air pollution control systems; cement aggregates; building materials	Suppl. 7 (1987)	Sufficient	Sufficient	Mesothelioma[d]
Silica, crystalline	Granite and stone industries; ceramics, glass, and related industries; foundries and metallurgical industries; abrasives; construction; farming	Vol. 68 (1997b)	Sufficient	Sufficient	Lung[d]
Talc containing asbestiform fibers	Manufacture of pottery, paper, paint, and cosmetics	Suppl. 7 (1987)	Sufficient	Inadequate	Lung[d] Mesothelioma[d]
Wood dust	Logging and sawmill workers; pulp and paper and paperboard industry; woodworking trades (e.g., furniture industries, cabinetmaking, carpentry and construction); used as filler in plastic and linoleum production	Vol. 62 (1995b)	Sufficient	Inadequate	Nasal cavities and paranasal sinuses[d]
Metals and metal compounds					
Arsenic and arsenic compounds	Nonferrous metal smelting; production, packaging, and use of arsenic-containing pesticides; sheep dip manufacture; wool fiber production; mining of ores containing arsenic	Suppl. 7 (1987)	Sufficient	Limited	Skin[d] Lung[d] Liver (angiosarcoma)[e]
Beryllium	Beryllium extraction and processing; aircraft and aerospace industries; electronics and nuclear industries; jewelers	Vol. 58 (1993a)	Sufficient	Sufficient	Lung[d]
Cadmium and cadmium compounds	Cadmium-smelter workers; battery production workers; cadmium-copper alloy workers; dyes and pigments production; electroplating processes	Vol. 58 (1993a)	Sufficient	Sufficient	Lung[d]
Chromium compounds, hexavalent	Chromate production plants; dyes and pigments; plating and engraving; chromium ferro-alloy production; stainless-steel welding; in wood preservatives; leather tanning; water treatment; inks; photography; lithography; drilling muds; synthetic perfumes; pyrotechnics; corrosion resistance	Vol. 49 (1990a)	Sufficient	Sufficient	Lung[d] Nasal sinuses[e]
Selected nickel compounds, including combinations of nickel oxides and sulfides in the nickel refining industry	Nickel refining and smelting; welding	Vol. 49 (1990a)	Sufficient	Sufficient	Lung[d] Nasal cavity and sinuses[d]
Wood and fossil fuels and their by-products					
Benzene	Production; solvents in the shoe production industry; chemical, pharmaceutical, and rubber industries; printing industry (rotogravure plants, bindery departments); gasoline additive	Suppl. 7 (1987)	Sufficient	Limited	Leukemia[d]
Coal tars and pitches	Production of refined chemicals and coal tar products (patent-fuel); coke production; coal gasification; aluminum production; foundries; road paving and construction (roofers and slaters)	Suppl. 7 (1987)	Sufficient	Sufficient	Skin[d] Lung[e] Bladder[e]

Continued next page

Appendix 1. Cont.

Table 3. Continued

Substance or mixture	Occupation or industry in which the substance is found[a]	*IARC Monograph* volume (year)[b]	Human evidence[c]	Animal evidence[c]	Site(s)
Mineral oils, untreated and mildly treated	Production; used as lubricant by metal workers, machinists, engineers; printing industry (ink formulation); used in cosmetics, medicinal and pharmaceutical preparations	Suppl. 7 (1987)	Sufficient	Inadequate	Skin[d] Bladder[e] Lung[e] Nasal sinuses[e]
Shale oils or shale-derived lubricants	Mining and processing; used as fuels or chemical-plant feedstocks; lubricant in cotton textile industry	Suppl. 7 (1987)	Sufficient	Sufficient	Skin[d]
Soots	Chimney sweeps; heating-unit service personnel; brick masons and helpers; building demolition workers; insulators; firefighters; metallurgical workers; work involving burning of organic materials	Vol. 35 (1985)	Sufficient	Inadequate	Skin[d] Lung[d] Esophagus[e]
Monomers					
Vinyl chloride	Production; production of polyvinyl chloride and co-polymers; refrigerant before 1974; extraction solvent; in aerosol propellants	Suppl. 7 (1987)	Sufficient	Sufficient	Liver (angiosarcoma)[d] Liver (hepato-cellular)[e]
Intermediates in plastics and rubber manufacturing					
Bis(chloromethyl) ether and chloromethyl methyl ether (technical grade)	Production; chemical intermediate; alkylating agent; laboratory reagent; plastic manufacturing; ion-exchange resins and polymers	Suppl. 7 (1987)	Sufficient	Sufficient	Lung (oat cell)[d]
Aromatic amine dyes					
4-Aminobiphenyl	Production; dyestuffs and pigment manufacture	Suppl. 7 (1987)	Sufficient	Sufficient	Bladder[d]
Benzidine	Production; dyestuffs and pigment manufacture	Suppl. 7 (1987)	Sufficient	Sufficient	Bladder[d]
2-Naphthylamine	Production; dyestuffs and pigment manufacture	Suppl. 7 (1987)	Sufficient	Sufficient	Bladder[d]
Pesticides					
Ethylene oxide	Production; chemical industry; sterilizing agent (hospitals, spice fumigation)	Vol. 60 (1994)	Limited	Sufficient	Leukemia[d]
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)	Production; use of chlorophenols and chlorophenoxy herbicides; waste incineration; PCB production; pulp and paper bleaching	Vol. 69 (1997a)	Limited	Sufficient	All sites combined[d] Lung[e] Non-Hodgkin lymphoma[e] Sarcoma[e]
Others					
Aflatoxin	Feed production industry; workers loading and unloading cargo; rice and maize processing	Vol. 82 (2002b)	Sufficient	Sufficient	Liver[d]
Involuntary (passive) smoking	Workers in bars and restaurants; office workers	Vol. 83 (2004)	Sufficient	Sufficient	Lung[d]
Mustard gas	Production; used in research laboratories; military personnel	Suppl. 7 (1987)	Sufficient	Limited	Larynx[d] Lung[e] Pharynx[e]
Strong inorganic-acid mists containing sulfuric acid	Pickling operations; steel industry; petrochemical industry; phosphate acid fertilizer manufacturing	Vol. 54 (1992a)	Sufficient	Not available	Larynx[d] Lung[e]

[a]Not necessarily an exhaustive list of occupations/industries in which this agent is found; not all workers in these occupations/industries are exposed. The term "production" is used to indicate that this substance is man-made and that workers may be exposed in the production process. [b]Most recent IARC evaluation; for those referenced to Supplement 7 (IARC 1987), it is possible that the 1987 review was quite perfunctory and that the essential evidence was cumulated at an earlier date. [c]As judged by the IARC working group; we added the notation "not available" to signify those substances for which there was no evidence at all. [d]We judged that evidence for an association with this site was strong. [e]We judged that evidence was suggestive.

Appendix 2. Occupations or industries evaluated by IARC as definitely, probably, or possibly entailing excess risk of cancer among workers.

Source: Siemiatycki et al. Listing occupational carcinogens. Environmental Health Perspectives. 112(15):1447-57, Nov 2004.

Table 6. Occupations or industries that have been evaluated by IARC as definitely (group 1), probably (group 2A), or possibly (group 2B) entailing excess risk of cancer among workers.

Occupation or industry	Suspected substance	*IARC Monograph* volume (year)[a]	Group	Site(s)
Aluminum production	Pitch volatiles; aromatic amines	Suppl. 7 (1987)	1	Lung,[b] bladder[b]
Auramine manufacture	2-Naphthylamine; auramine; other chemicals; pigments	Suppl. 7 (1987)	1	Bladder[b]
Boot and shoe manufacture and repair	Leather dust; benzene and other solvents	Suppl. 7 (1987)	1	Leukemia,[b] nose,[b] paranasal sinuses,[b] bladder[c]
Carpentry and joinery	Wood dust	Suppl. 7 (1987)	2B	
Coal gasification	Coal tar; coal-tar fumes; PAHs	Vol. 34 (1984)	1	Skin (including scrotum),[b] bladder,[b] lung[b]
Coke production	Coal-tar fumes	Suppl. 7 (1987)	1	Skin (scrotum),[b] lung,[b] bladder,[c] kidney[c]
Dry cleaning	Solvents and chemicals used in "spotting"	Vol. 63 (1995a)	2B	
Furniture and cabinet making	Wood dust	Suppl. 7 (1987)	1	Nose and sinonasal cavities[b]
Hairdressers and barbers	Dyes (aromatic amines, amino-phenols with hydrogen peroxide); solvents; propellants; aerosols	Vol. 57 (1993b)	2A	Bladder,[c] lung,[c] non-Hodgkin lymphoma,[c] ovary[c]
Hematite mining, underground, with radon exposure	Radon daughters; silica	Suppl. 7 (1987)	1	Lung[b]
Iron and steel founding	PAHs; silica; metal fumes; formaldehyde	Suppl. 7 (1987)	1	Lung[b]
Isopropanol manufacture, strong-acid process	Diisopropyl sulfate; isopropyl oils; sulfuric acid	Suppl. 7 (1987)	1	Paranasal sinuses,[b] larynx,[b] lung[c]
Magenta manufacture	Magenta; *ortho*-toluidine; 4,4´-methylene bis(2-methylaniline); *ortho*-nitrotoluene	Vol. 57 (1993b)	1	Bladder[b]
Painters		Vol. 47 (1989c)	1	Lung,[b] bladder,[c] stomach[c]
Petroleum refining	PAHs	Vol. 45 (1989b)	2A	Bladder,[c] brain,[c] leukemia[c]
Printing processes	Solvents; inks	Vol. 65 (1996)	2B	
Production of art glass, glass containers, and pressed ware	Lead; arsenic; antimony oxides; silica; asbestos; other metal oxides; PAHs	Vol. 58 (1993a)	2A	Lung[c]
Rubber industry	Aromatic amines; solvents	Suppl. 7 (1987)	1	Bladder,[b] stomach,[c] larynx,[c] leukemia,[c] lung[c]
Textile manufacturing industry	Textile dust in manufacturing process; dyes and solvents in dyeing and printing operations	Vol. 48 (1990b)	2B	

[a]Most recent IARC evaluation; for those referenced as Supplement 7 (IARC 1987), it is possible that the 1987 review was quite perfunctory and that the essential evidence was cumulated at an earlier date. [b]We judged that the evidence for an association with this site was strong. [c]We judged that the evidence was suggestive.

Appendix 3. Definite or probable occupational carcinogens and carcinogenic circumstances, by site.

Source: Siemiatycki et al. Listing occupational carcinogens. *Environmental Health Perspectives*. 112(15):1447-57, Nov 2004.

Table 7. Definite or probable occupational carcinogens and carcinogenic circumstances, by site.

Site	Strength of evidence[a]	High-risk substance or circumstance
Pharynx and nasopharynx	Suggestive	Mustard gas; formaldehyde
Nasal cavities and paranasal sinuses	Strong	Boot and shoe manufacture and repair; furniture and cabinet making; isopropanol manufacture, strong acid process; selected nickel compounds, including combinations of nickel oxides and sulfides in the nickel-refining industry; wood dust
	Suggestive	Chromium compounds, hexavalent; formaldehyde; mineral oils, untreated and mildly treated
Esophagus	Suggestive	Soots; tetrachloroethylene
Stomach	Suggestive	Painters; rubber industry
Gastrointestinal tract	Suggestive	Asbestos
Liver and biliary tract	Strong	Aflatoxin; ionizing radiation
	Suggestive	Polychlorinated biphenyls; trichloroethylene
Liver (angiosarcoma)	Strong	Vinyl chloride
	Suggestive	Arsenic and arsenic compounds
Liver (hepatocellular)	Suggestive	Vinyl chloride
Pancreas	Suggestive	Acrylamide
Larynx	Strong	Isopropanol manufacture, strong acid process; inorganic acid mists containing sulfuric acid; mustard gas
	Suggestive	Asbestos; rubber industry
Lung	Strong	Aluminum production; arsenic and arsenic compounds; asbestos; beryllium; cadmium and cadmium compounds; chromium compounds, hexavalent; coal gasification; coke production; hematite mining, underground, with radon exposure; involuntary (passive) smoking; ionizing radiation; iron and steel founding; selected nickel compounds, including combinations of nickel oxides and sulfides in the nickel refining industry; painters; silica, crystalline; soots; talc containing asbestiform fibers
	Suggestive	Benz[*a*]anthracene; benzo[*a*]pyrene; α-chlorinated toluenes; coal tars and pitches; dibenz[*a,h*]anthracene; diesel engine exhaust; epichlorohydrin; hairdressers and barbers; inorganic acid mists containing sulfuric acid; isopropanol manufacture (strong acid process); mineral oils (untreated and mildly treated); nonarsenical insecticides; mustard gas; production of art glass, glass containers, and pressed ware; rubber industry; TCDD
Lung (oat cell)	Strong	Bis(chloromethyl) ether and chloromethyl methyl ether (technical grade)
Bone	Strong	Ionizing radiation
Melanoma	Strong	Solar radiation
	Suggestive	Ultraviolet radiation (A, B and C) from artificial sources
Skin	Strong	Arsenic and arsenic compounds; Coal tars and pitches; coal gasification; coke production; dibenz[*a,h*]anthracene; mineral oils, untreated and mildly treated; shale oils or shale-derived lubricants; solar radiation; soots
	Suggestive	Benz[*a*]anthracene; benzo[*a*]pyrene; creosotes
Mesothelioma	Strong	Asbestos; erionite; talc containing asbestiform fibers
CNS	Suggestive	Epichlorohydrin
Sarcoma	Suggestive	TCDD
Cervix	Suggestive	Tetrachloroethylene
Ovary	Suggestive	Hairdressers and barbers
Kidney	Suggestive	Coke production
Kidney (renal cell)	Suggestive	Trichlorethylene
Bladder	Strong	Aluminum production; 4-aminobiphenyl; auramine manufacture; benzidine; coal gasification; magenta manufacture; 2-naphthylamine; rubber industry
	Suggestive	Benz[*a*]anthracene; benzidine-based dyes; benzo[*a*]pyrene; boot and shoe manufacture and repair; 4-chloro-*ortho*-toluidine; coal tars and pitches; coke production; dibenz[*a,h*]anthracene; diesel engine exhaust; hairdressers and barbers; 4,4′-methylene bis(2-chloroaniline); mineral oils, untreated and mildly treated; *ortho*-toluidine; painters; petroleum refining
Brain	Suggestive	Nonarsenical insecticides; petroleum refining
Thyroid	Strong	Ionizing radiation
Non-Hodgkin lymphoma	Suggestive	Hairdressers and barbers; nonarsenical insecticides; TCDD; tetrachloroethylene; trichloroethylene
Lympho-hematopoietic system	Suggestive	1,3-Butadiene
Multiple myeloma	Suggestive	Nonarsenical insecticides
Leukemia	Strong	Benzene; boot and shoe manufacture and repair; ethylene oxide; ionizing radiation
	Suggestive	Formaldehyde; nonarsenical insecticides; petroleum refining; rubber industry
Other sites	Suggestive	Ionizing radiation[b]
All sites combined	Strong	TCDD[c]

CNS, central nervous system; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin.
[a]Our judgment of strength of evidence regarding each site. [b]There is suggestive evidence of an effect of ionizing radiation on several sites in addition to those shown here. [c]The evidence for an association with TCDD only becomes strong when data are combined for all cancer sites.

Appendix 4. Mortality rates from cancer and heart disease for ages younger than 85 and 85 and older, 1975-2001.

Source: *CA: A Cancer Journal for Clinicians*. 55(1):10-30, Jan-Feb 2005.

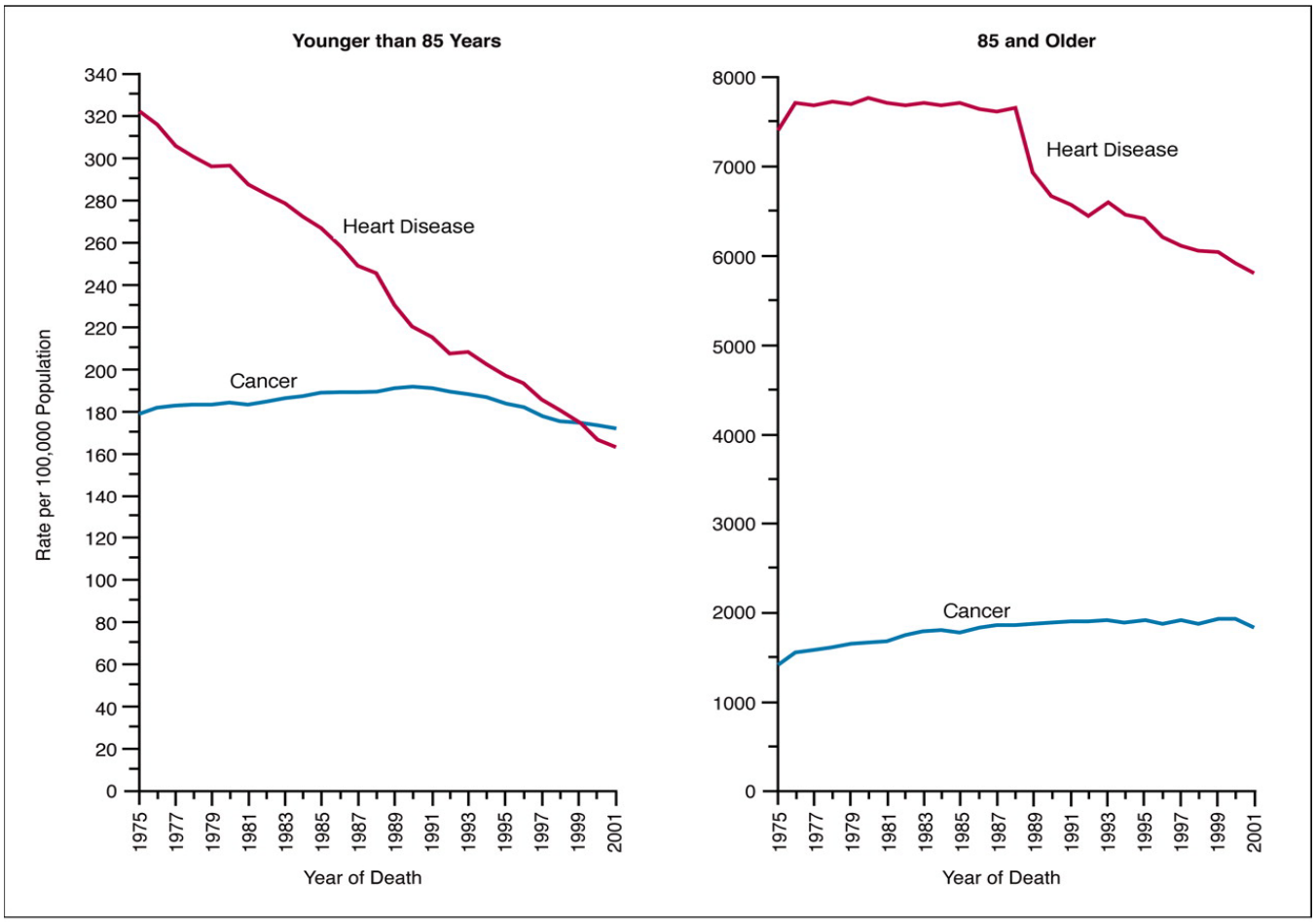
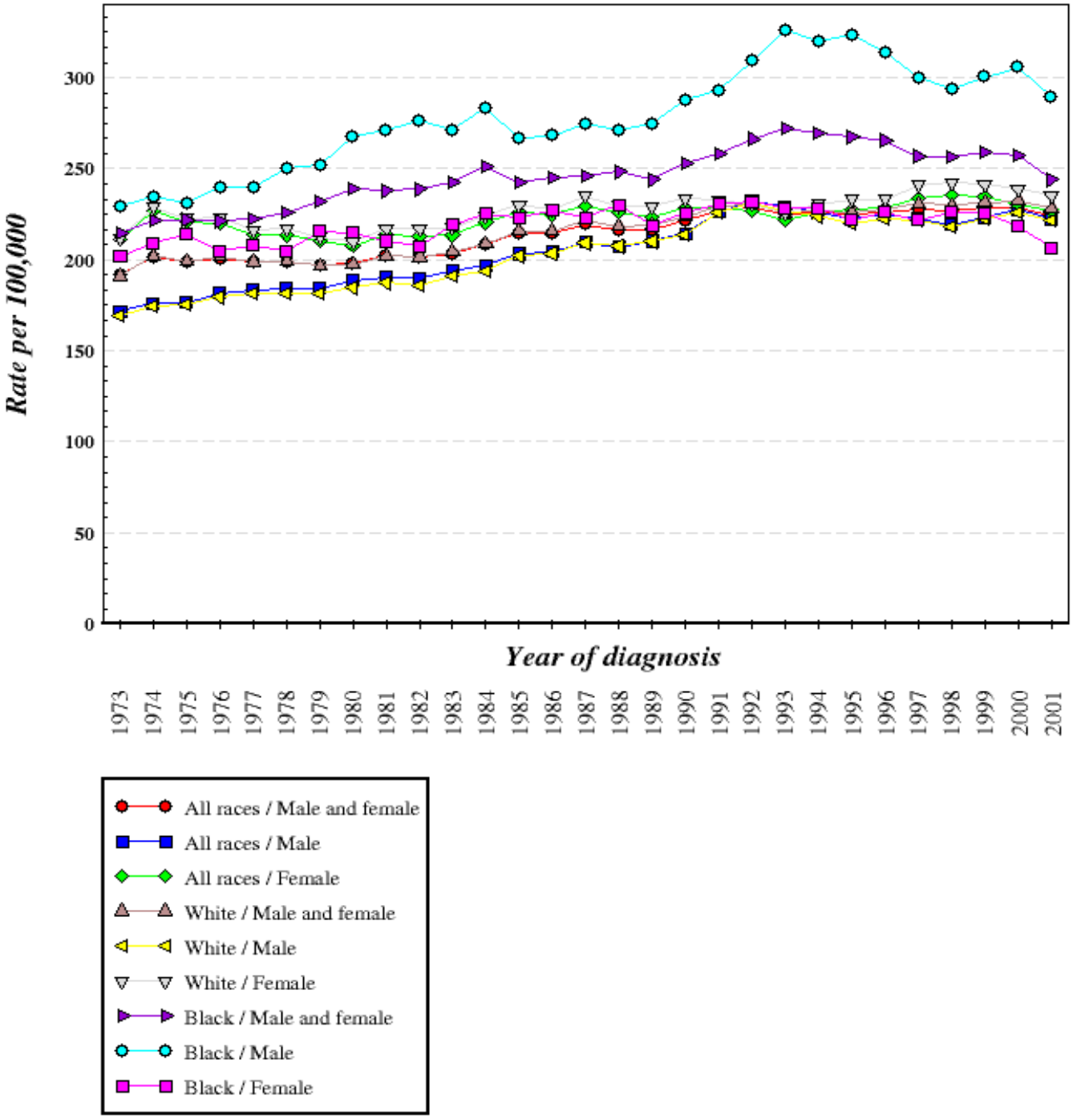


FIGURE **6** Death Rates* From Cancer and Heart Disease for Ages Younger than 85 and 85 and Older.
*Rates are age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes, 1960 to 2001, National Center for Health Statistics, Centers for Disease Control and Prevention, 2004.

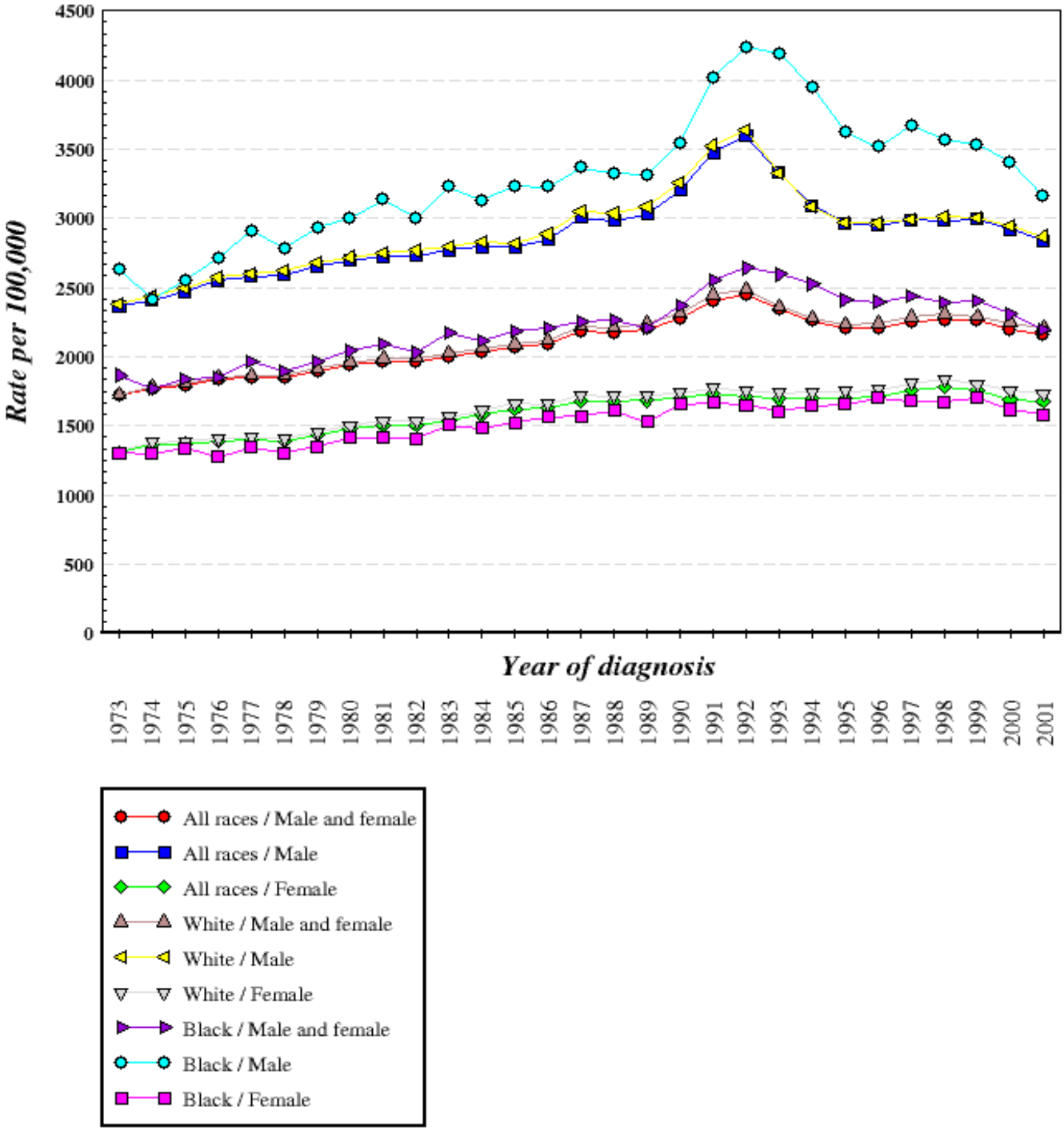
Appendix 5. Incidence rates for all cancer sites by race and sex for ages 64 and under, 1973-2001.

Source: SEER Cancer Query Systems, http://seer.cancer.gov/canques/



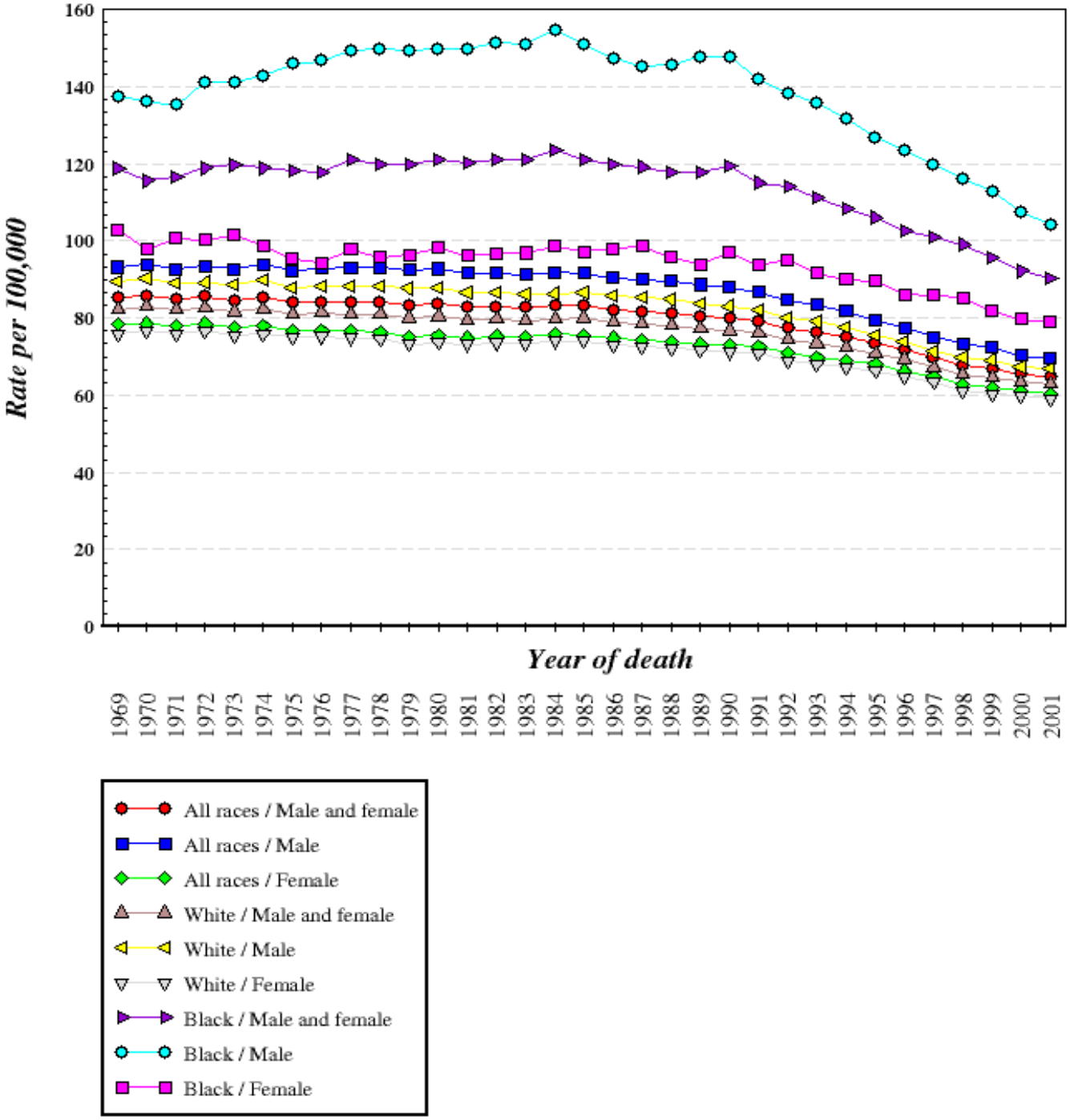
Appendix 6. Incidence rates for all cancer sites by race and sex for ages 65 and over, 1973-2001.

Source: SEER Cancer Query Systems, http://seer.cancer.gov/canques/



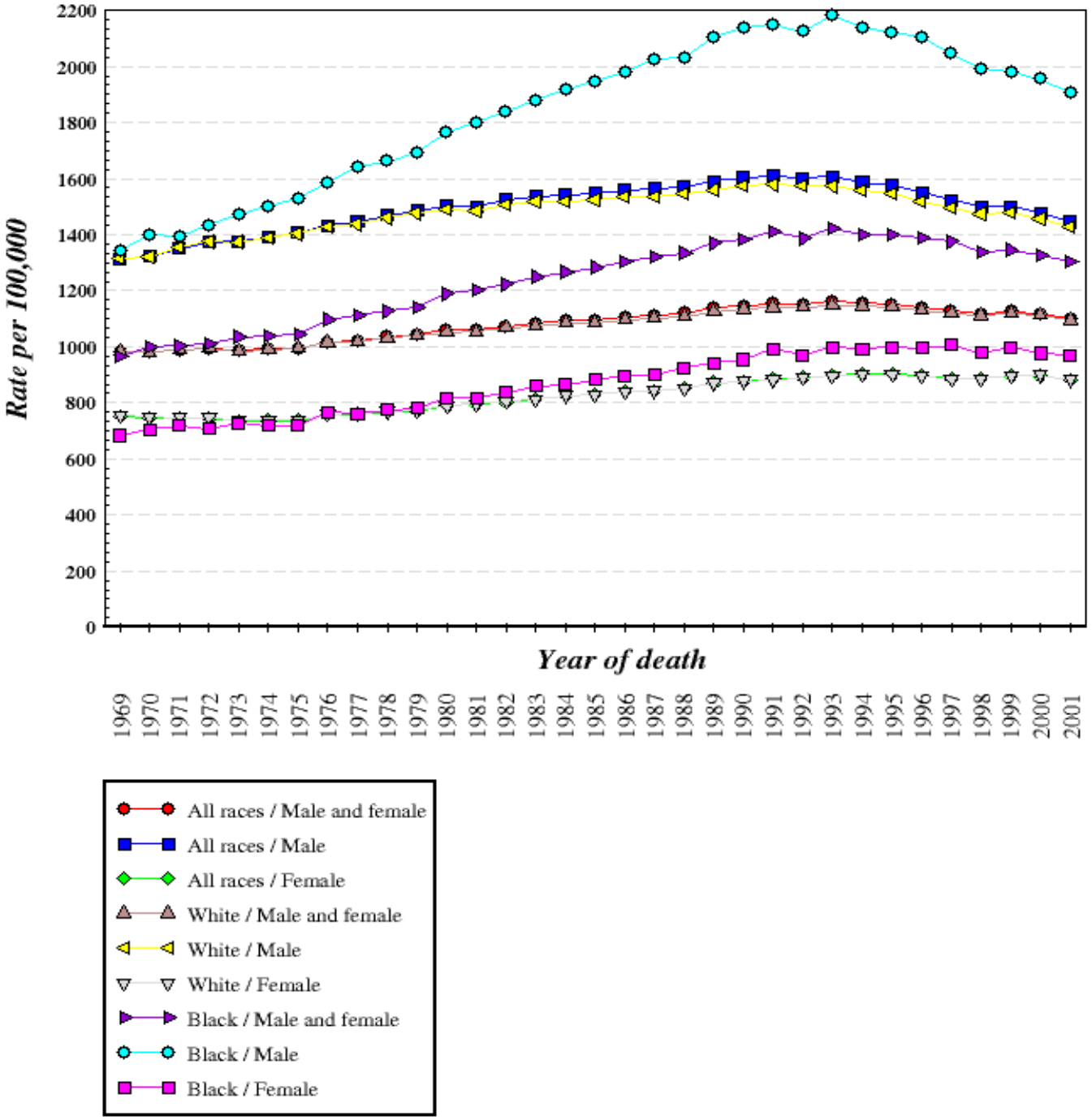
Appendix 7. Mortality rates for all cancer sites by race and sex for ages 64 and under, 1969-2001.

Source: SEER Cancer Query Systems, http://seer.cancer.gov/canques/



Appendix 8. Mortality rates for all cancer sites by race and sex for ages 65 and over, 1969-2001.

Source: SEER Cancer Query Systems, http://seer.cancer.gov/canques/



Appendix 9. Incidence rates for lung & bronchus cancers by race and sex, 1973-2001.

Source: SEER Cancer Query Systems, http://seer.cancer.gov/canques/