

Environmental and Occupational Causes of Cancer Re-visited

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ABSTRACT

We recently completed a review of scientific evidence, particularly epidemiologic evidence, regarding the contribution of environmental and occupational exposures to the overall cancer burden in the US. We evaluated the efforts to estimate the proportion of cancer due to these involuntary exposures, including the ambitious effort by Doll and Peto and an update by a group of authors at the Harvard Center for Cancer Prevention. In this paper, we critique these efforts, 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. We conclude 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. We support the new initiative in the European Union to evaluate chemicals more fully before they reach the market.

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INTRODUCTION

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 specific quantitative causal percentage. At the same time, scientific research has also made it clear that

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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 US 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 US, 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% due 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 (1).

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 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 (2). 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. (3) and Davis *et al.* (4) 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 co-workers 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 (3).

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 (5). 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 US. 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 (6). It reiterates the claim by Higginson 25 years earlier (7), 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 (6).

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

CURRENT VIEWS OF CANCER CAUSATION

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 (8). 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. 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) (9). 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 health intervention would be too complex to be of practical value” (10). 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 (9). 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. However, it is impossible to estimate how these components add up to a specific proportion of the total cancer burden in the US. 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.

TRENDS IN CANCER INCIDENCE AND MORTALITY

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 US 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. Cancer mortality for all sites declined somewhat in the 1990s, yet it has hovered around 200/100,000 for the past 60 years (12).

From 1950 to 2001, the incidence rate for cancer in all sites combined increased by 85%. 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 (13).

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 2,452/100,000 in 1992 and then declined to 2,196/100,000 in 2000. The cancer mortality rate for those under 65 years steadily declined from 86/100,000 in 1970 to 65/100,000 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 (14).

DISCUSSION

We summarized the evidence by selected cancer sites and by major categories of exposure. Evidence from epidemiologic studies was the focus of our review, given the importance it receives in considering causes of human cancer. We focused 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 did 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 (15).

We reviewed recent trends in rates for the cancers for females and males and for blacks and whites in the US (as explained above) and selected tables from Siemiatycki *et al.*, (16) and graphs of selected cancer data trends. We also relied upon the informative database “Chemical Contaminants and Human Disease” assembled by Janssen, Solomon, and Schettler and identified multiple categories of cancer types with the strongest scientific evidence of elevated risk due to environmental and occupational exposures (17). 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 to 2004. Further details of our review methods and results are available elsewhere (see <http://www.cheforhealth.org>).

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, 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. However, 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. 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 within a single generation. However, 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” (18). Cancer is now the second leading cause of death overall, and the first leading cause of death for Americans under the age of 85.

Incidence rates for some cancer sites, including lung, prostate, myeloma, thyroid cancer and non-Hodgkin’s lymphoma have increased particularly rapidly over the past half century. Looking at a more recent window, the list of 10 cancers fastest on the rise changes. From 1992 to 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% (19).

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 11–13 per 100,000. This increase cannot be attributed to improved diagnosis. 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 (20). Better control of *H. Pylori* infections also played a role in reducing stomach cancer.

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.

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 (20).

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 (20).

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 (20). 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 16.8/100,000 in 2000 and most of this increase occurred in the 1970s and 1980s (13).

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) (21).

A considerable portion of the evidence we reviewed 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 5 years working on top of coke ovens. The same study found that of the few white workers in this occupational category, a negligible portion died of lung cancer (22). 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 (3).

From 1972 through 2003, the International Agency for Research on Cancer (IARC) evaluated over 880 substances, complex mixtures, and industrial processes. 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 considered by IARC to definitely, probably, or possibly entail “excess risk of cancer among workers.” Siemiatycki and co-workers (16) also summarized the substantial cumulative evidence that occupational exposures cause many types of cancer.

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 4 miles of a Superfund site. According to the US 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 (23).” Most of the 1,241 sites on today’s National Priorities List did not exist prior to World War II. 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.

Since the US 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 US 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 nonindustrial sources (24)). 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 (25).

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" (26).

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;..." (27). Two months later, the Reagan administration nullified the rule (28).

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 Hueper, 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 (30).

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 (29).

CONCLUSIONS AND RECOMMENDATIONS

We believe that there is substantial evidence that occupational and environmental exposures contribute to the burden of cancer. As a result, there is a compelling need to continue efforts to avoid such exposures wherever feasible. We agree with Sandra Steingraber, author of *Living Downstream: An Ecologist Looks at Cancer and the Environment*, that the issue is not the precise magnitude of the dangers 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 (20).

At the same time, uncertainty and controversy are permanent features of scientific research. They must not deter us, however, 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 (31).

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 include 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 (32). The United States has much to learn from the REACH approach-regulation: 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 (20).”

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