Chemical Exposures in the Workplace
Effect on Breast Cancer Risk Among Women

by Suzanne M. Snedeker, PhD

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Breast cancer rates are highest in Western nations. The American Cancer Society estimates in the United States alone 212,920 women and 1,720 men will be diagnosed with breast cancer this year (American Cancer Society, 2006). Because more than half of all cases are largely unexplained by established risk factors, interest has increased in the role environmental factors, including chemical exposures and workplace environments, may play in breast cancer incidence.

However, this is an emerging area of research, and evidence is often fragmented. No adequate exposure assessment or epidemiologic studies evaluating health risks, including cancer risk, exist for most chemicals. During the past 10 to 20 years, human and animal studies have identified specific chemical exposures that may affect breast cancer risk. Much of what is known about chemicals and breast cancer risk has emerged from the occupational cancer literature. Researchers are also identifying occupations with higher rates of breast cancer. Further work is needed to determine whether chemical exposures may partly explain these higher rates.

This article is a road map for occupational health nurses interested in the risk of breast cancer in the workplace. It provides a brief overview of the biology of the breast and breast cancer and is then divided into three sections: history, current science, and future research. Occupational health nurses can use the current science regarding breast cancer risks in the workplace to provide risk communication for employees and their families. They can also serve as advocates for necessary research ultimately leading to risk reduction and prevention strategies in the workplace.

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OVERVIEW OF THE BIOLOGY OF THE BREAST AND BREAST CANCER

The breasts are unique because most of their development occurs after birth under the influence of circulating hormones and local growth factors. Breast ductal tissue starts to grow several years before the onset of menstruation and continues growing through puberty. Bud-like structures of mammary epithelial cells appear at the tips of the ducts. Under the influence of growth hormone, ovarian hormones, and a variety of local growth factors, a branched network of ducts forms, with the ducts growing through a matrix of fat and connective tissue called "stroma." Under the influence of hormones secreted during pregnancy, the breasts develop further and differentiate with the capacity to produce milk. During lactation, the ducts carry the milk to the nipples. The differentiation of breast cells confers some protection against breast cancer, explaining why women who have children earlier in life have a lower risk of breast cancer than women who delay having children or never have children (Medina, 2004; Russo, Mailo, et al., 2005; Russo, Moral, Balogh, Mailo, & Russo, 2005).

During the last part of the menstrual cycle, some breast cells divide in response to cyclic increases in estrogen and progesterone levels. Every time a breast cell divides, it makes a copy of its DNA. If a mistake is made during copying, a mutation (called a spontaneous or somatic mutation) can be passed on to daughter cells. Other mutations may be inherited (e.g., BRCA1 and BRCA2) or induced by chemical carcinogens. The accumulation of mutations in key genes controlling the ability of cells to divide, grow, and die may take many years. Accumulation of mutations may even start during gestation in the early stages of breast development. An "initiated" cell with a mutation looks the same as an adjacent normal cell but acts differently. It multiplies (called hyperplasia) and as the cell gains more mutations, develops an abnormal appearance and grows out of control, invading surrounding tissue. Cells acquiring additional mutations may escape the confines of the breast duct, traveling to other organs via blood or lymphatic vessels. When breast tumor cells invade another organ, the tumor has metastasized.

Factors consistently associated with increased breast cancer risk are listed in the Sidebar. Eighty to ninety percent of women with breast cancer have no close relatives with the disease. Established risk factors explain only 25% to 50% of breast cancer cases (Madigan, Zielger, Benichou, Byrne, & Hoover, 1995; Rockhill, Weinberg, & Newman, 1998).

HISTORY

Role of Environmental Risk Factors

Interest in the role environmental factors may play in breast cancer risk has emerged from diverse evidence. First, breast cancer rates vary widely geographically. The highest breast cancer rates are in North America (99.4 cases per 100,000 population [age adjusted]), followed by Western–Northern Europe and Australia–New Zealand (82.5 to 85 cases per 100,000 population [age adjusted]), and the lowest rates are in middle Africa (16.5 cases per 100,000 population [age adjusted) and China (18.7 cases per 100,000 population [age adjusted]) (Parkin, Bray, Ferlay, & Pisani, 2002). Reasons for this variation may include:

- Life expectancy.
- Screening and detection practices.
- Childbearing and reproductive patterns.
- Duration of breastfeeding.
- Differences in diet and lifestyle.
- Exposure to environmental chemicals.

Migration studies support a role for environmental factors influencing breast cancer risk. Women from rural Asia (with low breast cancer rates) who migrate to the United States have daughters and granddaughters with higher breast cancer rates. Within two generations, the breast cancer rates of the offspring of Asian immigrants were as high as those of Western white women (Shimizu et al., 1991).

Second, a Scandinavian study of twins found that although inherited factors accounted for 27% of breast cancer risk, 73% of risk was linked to environmental factors, suggesting environment plays a major role in determining breast cancer risk (Lichtenstein et al., 2000).

Current research is evaluating the roles exercise, diet, obesity, alcohol use, hormone replacement therapy use, oral contraceptive use, and environmental chemicals play in breast cancer incidence. This article primarily focuses on how exposure to chemicals encountered in the workplace may affect breast cancer risk in women. It also considers occupations with a higher breast cancer risk for which there is currently no known chemical association.

Health Hazards and Chemical Exposures

In 1995, the Office of Technology Assessment submitted a report to the U.S. Congress entitled "Screening and Testing Chemicals in Commerce" (Office of Technology Assessment, 1995). The report documented the paucity of toxicologic studies and health effects data for chemicals used in commerce. Approximately 70,000 chemicals have been in use since 1976. An estimated 1,000 to 2,000 additional chemicals are produced per year, bringing the potential total number of chemicals produced to more than 100,000. According to the Office of Technology Assessment report, in 1984 the National Research Council estimated toxicologic testing data were available for only 20% of all chemicals used in commerce, and only 10% of the chemicals had data adequate to assess health hazards. By the mid-1990s, only 2% of all existing chemicals had been fully reviewed by the Environmental Protection Agency (Office of Technology Assessment, 1995).

Information has come from studies assessing cancer hazards using animal models. The National Toxicology Program has developed more than 538 technical reports on chemicals tested in its long-term animal cancer bioassay program (National Toxicology Program, 2006b). The Carcinogenicity Potency Database, established by the University of California at Berkeley, includes international cancer hazard testing data from animal models for approximately 1,500 chemicals (Carcinogenicity Potency Database, 2006).

Estimates of the number of employees in the United States, including females, exposed to chemicals in the workplace were compiled by the National Institute for Occupational Safety and Health (NIOSH) as part of the National Occupational Exposure Survey conducted from 1981 to 1983 (NIOSH, 2006). For instance, the database contains 14 pages of data on occupations in which workers are potentially exposed to the chemical benzene. Because breast cancer has a long latency, the original survey from the 1980s provides important historical data of potential past workplace exposures to chemicals among women. This information, together with known cancer hazard data, is useful for prioritizing potential at-risk occupations requiring further study. The online National Occupational Exposure Survey database provides an alphabetical index of chemical names linked to occupations within the Standard Industrial Classification code at www.cdc.gov/noes/noes4/agtindx3.html. NIOSH is planning to conduct the National Exposures at Work Survey, a

Factors Consistently Associated With Increased Breast Cancer Risk

- Advancing age
- Female gender
- Early onset of menstruation
- Late menopause
- Older age (> 30 years) at birth of first child or not having children
- Having a close relative with breast cancer
- Certain benign breast diseases (atypical hyperplasia)

study of chemical exposures in representative industries, starting with health care.

It is logical, when exploring the role chemicals may play in cancer risk, to examine cancer risks in populations with potentially the highest exposures, including worker exposures. The International Agency for Research on Cancer recently published an analysis of its database of 880 chemicals and workplace situations. It reported evidence of occupational links to 28 chemicals known to cause cancer in humans, 27 chemicals probably causing cancer, and 113 chemicals that are possible carcinogens (Siemiatycki et al., 2004). However, most of these studies evaluated the cancer risk of men in the work force. Why women have received less attention and been included less often than men in occupational epidemiologic studies of cancer is not known. Women's marginalization in many levels of society may have influenced past scientific directions.

Historical Trends in Cancer Risk Among Women in the Workplace

In the early 1700s, the Italian physician Bernardino Ramazzini observed breast cancer was more common in single women who were celibate members of religious orders than in married women (Huff, 2000). Thus, nulliparity was one of the first risk factors associated with breast cancer. Biological explanations for the protection conferred by an early full-term pregnancy and lactation remain an active area of investigation (Medina, 2004; Russo, Mailo, et al., 2005; Russo, Moral, et al., 2005).

Studies of cancer risk among women entering the work force after World War I and World War II are relatively rare (Zahm & Blair, 2003). Higher rates of lung cancer were observed in women who were radium purification workers. Studies documenting higher bone and breast cancer rates in women who were radium dial painters in the 1920s were not completed until the 1980s (Adams & Brues, 1980; Stebbings, Lucas, & Stehney, 1984). These young women whetted the radium-coated brushes to get a fine tip, thus ingesting radium.

Possible linkages between reproductive history and chemical exposures affecting breast cancer risk were identified among unmarried female chemists (Walrath, Li, Hoar, Mead, & Fraumeni, 1985). These female chemists, who had not had children, had higher rates of breast cancer, illustrating how the biology of the breast can affect susceptibility to carcinogenic chemicals. Animal studies suggest mammary glands in young virgin animals are less efficient at repairing damage to DNA caused by chemical carcinogens than those of animals having a full-term pregnancy early in life. Exposure of the breasts to hormones during pregnancy causes physiologic changes to them that are known to be protective against breast cancer (Medina, 2004). The biological changes the breasts undergo during pregnancy are complex and the subject of ongoing research. However, as the study of unmarried female chemists illustrates, women who are exposed to chemicals in the workplace and delay childbearing or are nulliparous may have a higher risk of breast cancer than women with similar exposures who have children by age 20.

Despite these reports of occupational cancer risk, such studies of women have been lacking since World War II. Some of the most poignant observations on the lack of inclusion of women were made in a series of papers by Zahm and colleagues from the National Cancer Institute. This included analysis of the design of more than 1,200 occupational cancer studies published from 1971 to 1990. Of these studies, only 14% presented an analysis of cancer risk in white women, and only 2% included analyses of cancer risk among non-white women (Zahm, Pottern, Lewis, Ward, & White, 1994). The International Commission on Occupational Health held its first conference on work-related diseases in 1906—100 years ago (International Commission on Occupational Health, 2006). Yet National Cancer Institute scientists, in reviewing occupational cancer risk in women, noted the first international scientific conference specifically devoted to this subject was not held until 1993 (Zahm & Blair, 2003).

Scientists at the National Cancer Institute have noted several reasons to study occupational cancers in women (Blair, Zahm, & Silverman, 1999; Zahm & Blair, 2003; Zahm, Ward, & Silverman, 2000):

1. Certain cancers occur primarily (breast cancer) or exclusively (ovarian, uterine, and cervical cancers) in women.

2. Men and women have distinct biological differences influencing absorption, metabolism, storage, and excretion of chemicals. Women have proportionally more fat than men, with a higher capacity to store fat-soluble chemicals. Women also have thinner skin and smaller lung volume, body surface area, and water volume. In addition, their chemical detoxification systems may be altered compared with men because hepatic cytochrome P450 enzymes are affected by cyclic female hormones (Blair et al., 1999; Greenberg & Dement, 1994; Zahm et al., 2000). Animal cancer bioassays conducted by the National Toxicology Program yielded evidence of gender differences in susceptibility to certain cancer-causing chemicals (Huff, 2000).

3. The percentage of women working outside the home has risen dramatically in the past 50 years. In 1950, women comprised 32% of the civilian work force. By 2003, this figure had doubled; 66.2% of single women and 61.0% of married women were employed. Significant changes have also occurred among women with children. In 1950, only 12% of women with children younger than 6 years were employed. By 2003, this had risen to 70.2% of single women and 59.8% of married women. By 2003, more than three-fourths of all women in the United States with school-aged children (6 to 17 years old) were employed (U.S. Census Bureau, 2004; Wagener et al., 1997).

4. The percentage of women within specific occupations is changing. The number of women employed in skilled trades in the United States increased threefold from 1960 to 1980, but recent changes in globalization have shifted manufacturing sector jobs from the United States to China, other parts of Asia, and Eastern Europe. Whereas women in Poland and China represent 60% and 90% of the work force in manufacturing sectors, respec-

tively, women in the United States comprise only 12% of the employees in manufacturing (Zahm et al., 2000). For new industries such as electronics and semiconductors, women comprise most of the work force worldwide. Possible health effects related to chemical exposures in these industries are just beginning to receive attention (Kennedy & Koehoorn, 2003; Messing et al., 2003; Pottern et al., 1994; Quinn, Woskie, & Rosenberg, 1995; Zahm & Blair, 2003).

CURRENT SCIENCE

In this section, examples of key research studies are given to illustrate current consensus on chemical exposures identified as increasing breast cancer risk in humans and animals. Studies are compared and contrasted to note similarities as well as differences in the evidence supporting chemical associations.

Human Epidemiologic Studies

Many early research studies on workplace chemical exposures and breast cancer were based on the cancer mortality study conducted by Cantor and colleagues at the National Cancer Institute. Women working with organic solvents (including methylene chloride, formaldehyde, and carbon tetrachloride), styrene, metals and metal oxides, lead and lead oxides, and acid mists had a higher risk of dying of breast cancer. Although there were limitations to this study, including lack of control for other factors affecting breast cancer risk, other studies have confirmed many of these associations (Cantor, Stewart, Brinton, & Dosemeci, 1995), including the association of breast cancer risk with organic solvent exposure. Elevated breast cancer risk has been observed in Danish women employed in the five top industries using organic solvents, including women employed for at least 1 year in textile, chemical manufacturing, paper and printing, and metal products industries (Hansen, 1999). For many of these industries, other chemical exposures may have contributed to breast cancer risk (e.g., exposure to metal mists and dyes). Scientists have also reported elevated breast cancer risks in Chinese and Swedish women exposed to organic solvents in the workplace (Petralia et al., 1998; Pollán & Gustavsson, 1999).

Although exposure to ethylene oxide has been shown to cause mammary tumors in rodent studies (Dunnick, Elwell, Huff, & Barrett, 1995), evidence of occupational exposures affecting breast cancer risk has not been consistent. Ethylene oxide has been used to sterilize instruments in veterinary and human health care settings and reduce the microbial load on spices and seasonings and archival materials. Ethylene oxide is also used in manufacturing cosmetic ingredients and has been found as a low-level contaminant in skin care products (Filser, Kreuzer, Greim, & Bolt, 1994). Although one small study of female workers in an ethylene oxide manufacturing plant reported a higher rate of breast cancer deaths (Norman, Berlin, Soper, Middendorf, & Stolley, 1995), a larger study did not (Steenland et al., 1991). British researchers did not observe a higher rate of breast cancer deaths among women exposed in the chemical industry or in hospital sterilization facilities (Coggon, Harris, Poole, & Palmer, 2004). However, more recent studies have reported a positive trend for higher breast cancer mortality (Steenland, Stayner, & Deddens, 2004) and incidence (Steenland, Whelan, Deddens, Stayner, & Ward, 2003) in women with many years of exposure (15 to 20 years latency) to ethylene oxide. These results illustrate why a latency effect must be considered when evaluating breast cancer risk in occupational studies. Other studies have questioned whether excessive ethylene oxide exposure from leaky sterilization equipment may partially explain a cluster of cancers, including breast, among pediatric nurses in Hungary (Kardos et al., 2003; Tompa, Major, & Jakab, 1999). More extensive research is needed to document whether an increased risk of cancers exists among workers exposed to ethylene oxide.

Although farmers are known to have a lower overall cancer risk than the general population, a higher risk of lip, skin, stomach, brain, and prostate cancer and lymphoma has been observed for agricultural workers (Blair & Zahm, 1995). Sunlight exposure and ultraviolet radiation have been linked to skin and lip cancer, but less is known about pesticide use and cancer risk in farm workers. The insecticide DDT was used extensively in the 1960s on cotton crops in the southeastern United States, but no studies are available evaluating breast cancer risk among female farm workers who picked or processed treated cotton (International Agency for Research on Cancer, 1974; Woodwell, Craig, & Johnson, 1971). Although DDT was banned during the late 1970s, its persistent breakdown product, DDE, can bio-concentrate in the fat of animals, fish, and humans. DDT is a known estrogen mimic, but DDE is weakly estrogenic. This may be one reason why most studies in the general population have not seen an association between blood or fat levels of DDE and breast cancer risk (Lopez-Cervantes, Torres-Sanchez, Tobias, & Lopez-Carrillo, 2004; Snedeker, 2001). Studies need to evaluate breast cancer risk in countries where DDT is still used for malaria control or among cotton workers in the United States exposed to DDT (Snedeker, 2001).

The long-term Agricultural Health Study is evaluating whether use of 50 different pesticides affects the cancer risk of 85,000 farm men and women from Iowa and North Carolina. Although few of the registered pesticide applicators are women, 26% of the wives from North Carolina and 33% of those from Iowa applied pesticides as part of their farm duties (Kirrane, Hoppin, Umbach, Samanic, & Sandler, 2004). Farm families may also be exposed to pesticides through drift, well water contamination, and handling or laundering of clothes worn during pesticide application. A preliminary assessment among 30,354 women enrolled in the study suggested their husbands' use of several types of pesticides moderately increased their breast cancer risk (Engel et al., 2005). Breast cancer risk increased approximately twofold in women whose husbands used 2,4,5-TP, a phenoxy herbicide no longer in use that was contaminated with the carcinogen dioxin. Increased breast cancer risk was also observed with husbands' use of the persistent organochlorine insecticide dieldrin (no longer in use) and the fungicide captan (currently in use). Diazinon, an organophosphate insecticide used against crop pests found in soil, was also associated with a higher breast cancer risk when used by husbands, but only in wives with a family history of breast cancer. This suggests a genetic–environmental interaction may be involved. Women's use of several organophosphate insecticides (chlorpyrifos, dichlorvos, and turbofos) was associated with a 2- to 2.6-fold increase in breast cancer risk among those who were premenopausal. As the number of cancer cases increases in this cohort, the researchers will publish revised analyses to determine whether these preliminary observations are confirmed.

Although certain occupations have been linked with higher breast cancer risk, the specific chemical exposures and practices responsible often have not been identified. For instance, a doubling of breast cancer risk was observed in Finnish registered nurses, pediatric nurses, midwives, and dental nurses (Sankila, Karjalainen, Läärä, Pukkala, & Teppo, 1990). A doubling of breast cancer risk was found for pediatric, psychiatric, surgical, medical, geriatric, and primary care nurses in Iceland. Further analysis in the Icelandic study indicated the highest risks were among nurses handling cytotoxic drugs (Gunnarsdóttir, Aspelund, Karlsson, & Rafnsson, 1997). Elevations in breast cancer risk also have been reported for nurses, dentists, and physicians in Denmark (Rix & Lynge, 1996) and among physicians and registered nurses in Sweden (Pollán & Gustavsson, 1999). These findings are in contrast to those of studies on breast cancer risk among nurses in the United States. Habel et al. (1995) did not observe a significant elevation in breast cancer risk among nurses from Washington State. A case–control study of nurses in western New York did not detect a higher breast cancer risk (Petralia et al., 1999). However, unlike the European studies, these studies did not compare registered nurses with practical nurses or nursing subspecialties. Although a variety of cancer-causing agents including chemotherapeutic agents, cytotoxic drugs, hormone-containing pharmaceutical agents, benzene, formaldehyde, and ethylene oxide have been used in veterinary and human health care, specific exposures to them according to specialty or job task have not been adequately evaluated (Gunnarsdóttir & Rafnsson, 1995).

Animal Cancer Bioassays for Chemical Hazard Identification

Adequate epidemiology studies of women in the workplace do not exist for many chemical exposures. The National Toxicology Program uses long-term studies of chemical exposures in laboratory rodents (mice and rats) to identify chemical carcinogens potentially posing a health risk to humans (Huff, 2000). More than 42 chemicals have been identified as mammary carcinogens in these animal cancer bioassays (Bennett & Davis, 2002; Dunnick et al., 1995). They include:

- Organic solvents.
- Dyes and dye intermediates.
- Chemicals used in the manufacture of rubber, synthetic rubber, and polyurethane foams.
- Certain flame retardants.
- A food additive.
- Lead scavengers added to gasoline.
- A metal used in microelectronics.
- Ethylene oxide used in sterilizing health-related instruments.
- A mold toxin called ochratoxin A.
- Several pesticides.
- A variety of pharmaceutical agents.
- A type of rocket fuel.

A searchable database of these chemicals is available at http://envirocancer.cornell.edu/eccd. In addition to specifying major uses and cancer classification, the database provides information on whether specific chemicals are still produced and their use in manufacturing and consumer products.

Specific Occupations Associated With Higher Breast Cancer Risk

Several large-scale studies have shed additional light on the types of occupations associated with higher breast cancer risk. Most of these studies have not assessed actual chemical exposures. One of the largest cohorts was established in Sweden. Pollán and Gustavsson observed 1,101,669 female employees for 19 years (from 1971 to 1989). In this study, mortality from breast cancer was significantly higher in physicians, nurses, dentists, midwives, pharmacists, and metal plate workers—all occupations with potential exposures to carcinogenic chemicals. However, mortality from breast cancer was also elevated for system analysis personnel, bookkeepers, bank tellers, secretaries, typists, clerical workers, and telephone and telegraph operators—occupations with little evidence of possible chemical linkages to cancer (Pollán & Gustavsson, 1999).

China historically has had one of the lowest rates of breast cancer in the world (Parkin et al., 2002). The Shanghai Breast Cancer Study used the Shanghai Cancer Registry and the Chinese Third National Census to examine breast cancer risk by occupation from 1980 to 1984, when relatively few controls limited chemical exposures in either industrial or professional settings (Petralia et al., 1998). Many of the occupations associated with higher breast cancer risk among urban Chinese workers are similar to those cited in North American and Scandinavian studies. The Shanghai study identified scientific researchers and laboratory technicians, physicians and nurses, electrical workers, workers exposed to organic solvents (especially benzene), and workers weaving and knitting in the textile industry, which is also known to have exposures to organic solvents, as having a higher breast cancer risk. This study also found a higher breast cancer risk among women working in rubber and plastic manufacturing industries. Many of the chemicals used in these industries have been identified as mammary carcinogens in National Toxicology Program animal cancer bioassays (Bennett & Davis, 2002; Dunnick et al., 1995). Teachers, librarians, clerical workers, administrative clerks, accountants, and bookkeepers also had elevated breast cancer risk (Petralia et al., 1998). Studies attempting to discern whether chemical exposures may exist among teachers to explain higher breast cancer risk are discussed later in this article.

The Shanghai and other epidemiologic studies observed a consistent, positive association between breast cancer risk and higher socioeconomic status. Possible reasons for this association include:

- More years of education.
- Delayed childbearing.
- A more sedentary lifestyle.
- Possible detection bias.
- In the United States, a higher percentage of individuals have insurance coverage and access to cancer screening.

Other possible influences suggested, but not explored, include:

- Lifestyle differences (e.g., social drinking [alcohol consumption is associated with higher breast cancer risk]).
- Greater use of dry cleaning.
- Building materials used in offices or residences.

Higher breast cancer risk or higher breast cancer mortality has been documented in teachers worldwide, including in the United States (Habel et al., 1995; Morton, 1995; Reynolds, Elkin, Layefsky, & Lee, 1999; Robinson & Walker, 1999; Williams, Stegens, & Goldsmith, 1977), China (Petralia et al., 1998), Sweden (Pollán & Gustavsson, 1999), Canada, the former Soviet Union, and the Netherlands (Goldberg & Labrèche, 1996). Higher education level and subsequent delayed childbearing is a possible explanation for the higher risk of breast and gynecologic cancers in teachers.

However, a large-scale study among California teachers is investigating whether environmental or lifestyle factors may partially explain elevated cancer risk in this occupation. The prospective California Teachers Study, evaluating cancer risk in 133,479 retired teachers and administrators, has reported a 51% higher incidence of breast cancer and elevated risk of ovarian cancer (28%), non-Hodgkin's lymphoma (53%), melanoma (59%), and uterine cancer (72%) (Bernstein et al., 2002).

Two environmental factors, smoking tobacco and living near areas of high pesticide use, have been investigated in the California Teachers Study cohort to determine whether they influence cancer risk. Breast cancer risk was not significantly higher in former smokers compared with never smokers. However, breast cancer risk was significantly elevated in current smokers and in non-smokers exposed to secondhand smoke compared with never smokers who were unexposed to secondhand smoke. Breast cancer risk was elevated in those who started smoking before 20 years old and in those who smoked heavily for long periods (Reynolds, Hurley, Goldberg, Anton-Culver, et al., 2004). Therefore, smoking is a modifiable breast cancer risk factor for teachers.

California's land use is heavily devoted to agriculture, and it has one of the most comprehensive pesticide-use reporting programs. The California Teachers Study investigators used geographic information systems methodology to determine whether pesticide use in agricultural areas was related to breast cancer risk among teachers living in these areas. This ecologic study was unable to find a relationship between residence in areas with high use of agricultural pesticides and breast cancer risk among teachers (Reynolds, Hurley, Goldberg, Yerabati, et al., 2004). Ecologic studies do not measure an individual's exposure to pesticides, but rather employ pesticide use in a geographic region as a surrogate measure. Because breast cancer has a long latency, recent pesticide use may not be as relevant as use closer to when a tumor may have started.

Non-Chemical Workplace Exposures

New evidence is emerging regarding individuals working the "graveyard" shift or rotating shifts having a higher risk of breast cancer than individuals working the day shift. Researchers hypothesized that "light at night" may suppress synthesis of the hormone melatonin. Animal studies have suggested suppression of melatonin synthesis from light at night may result in elevated blood levels of estrogen, an ovarian hormone associated with higher breast cancer risk (Stevens, 2002; Stevens & Rea, 2001). Recent studies of night-shift workers have partially supported this hypothesis. Individuals working the graveyard shift have a 1.6-fold higher risk of breast cancer (Davis, Mirick, & Stevens, 2001). Nurses working the graveyard shift for 30 or more years, or working rotating night shifts, have a similar moderate increase in breast cancer risk (Schernhammer et al., 2001). Use of residential light at night (i.e., turning on a night-light or a bedside lamp) does not appear to affect breast cancer risk in women (Davis et al., 2001).

Whether exposure to electromagnetic fields affects breast cancer risk has garnered interest. Although few women work in professions with exposures to high electromagnetic fields, evidence exists of a higher rate of breast cancer deaths among female telephone installers, repairers, and line workers and electrical workers. Most studies of women exposed to low electromagnetic fields have failed to detect an increase in breast cancer risk (Caplan, Schoenfeld, O'Leary, & Leske, 2000). However, a Canadian study reported a small increase in breast cancer risk among women in jobs exposed to low-frequency electromagnetic fields (Labreche et al., 2003). Residential exposure to electromagnetic fields (e.g., electric blanket use) does not appear to affect the risk of breast cancer (Davis, Mirick, & Stevens, 2002; Kabat et al., 2003).

FUTURE RESEARCH

Research needed to better evaluate occupational cancer risk among women falls into the following categories (Zahm et al., 2000):

- Studying occupations with potential exposures to identified chemical carcinogens.
- Developing methods to better characterize chemical exposures.
- More effectively characterizing chemical exposures by job type and task.
- Determining whether potential "gender" differences may affect the magnitude of chemical exposures.
- Using molecular approaches to identify gene–environment interactions.

Occupations With Exposures to Identified Chemical Carcinogens

As mentioned earlier, the National Toxicology Program has identified dozens of chemicals capable of inducing mammary tumors in laboratory animals (National Toxicology Program, 2006a). Most are still being made or used in manufacturing. In addition, for many occupations with potential exposures to carcinogens, health outcome data are limited to mortality linkage studies. More carefully designed case–control studies including collection of information on potential confounding factors, detailed history of job tasks, and potential chemical exposures are needed. Some employees with suspected exposures to carcinogens include (Zahm et al., 2000):

- Polyurethane, vinyl, and rubber and synthetic rubber manufacturing workers.
- Pharmaceutical and biomedical professionals.
- Flame-retardant manufacturing workers.
- Dry cleaner employees.
- Automobile and airline mechanics.
- Workers repairing and manufacturing computer and copier equipment.
- Firefighters.
- Print, dye, and textile workers.
- Cosmetologists and hair dressers.
- Metal workers and mechanics.
- Employees in semiconductor manufacturing and related electronic industries.

The electronics industry globally employs primarily women as its work force (Quinn et al., 1995). The solvent benzene and the metal indium phosphide are used to manufacture semiconductors, and both have induced mammary tumors in animal studies conducted by the National Toxicology Program (Bennett & Davis, 2002; Dunnick et al., 1995). Operational conditions, including use of recirculated air in "clean rooms" for semiconductor manufacture, may increase exposures to carcinogenic chemicals (Novak, 2003). A preliminary report assessing cancer risk among workers at National Semiconductor in the United Kingdom indicated breast cancer risk was doubled in female semiconductor workers employed after 1982 (McElvenny et al., 2003). Further studies are needed in European and North American plants to define exposures to suspect chemicals and fully characterize the cancer risk of female and male employees.

For professions with exposure to suspected carcinogens, further monitoring of employees is warranted, including collection of blood, urine, and exhaled breath samples for biomonitoring. Data on breast cancer risk factors such as childbearing and reproductive history, alcohol use, diet, hormone replacement therapy use, oral contraceptive use, tobacco use, obesity, and history of night-shift work should also be collected.

Occupations With a Higher Risk of Breast Cancer

Although breast cancer risk is elevated in teachers, librarians, and clerical workers worldwide, the potential exposure to carcinogenic chemicals in these professions has not been characterized. These occupations involve extensive handling of printed paper, yet little is known about transfer of dyes or inhalation of paper treatments. The solvent formaldehyde is used in paper finishing and in manufacturing carbonless paper, as well as in building materials ranging from ceiling tiles to a preservative in plywood and particle board (Etkin, 1996; Korhonen et al., 2004). Similarly, although some studies suggest nursing and other health care professions have a higher breast cancer risk, higher-risk subgroups exposed to cytotoxic drugs or viruses that may affect immune system responses have not been well studied.

Methods to Better Characterize Chemical Exposures

Development of biomarkers of exposures to chemicals is important for the study of occupational cancer risk to move forward. The National Cancer Institute has taken leadership in this area. The Agricultural Health Study is developing better methods to characterize pesticide exposures among farm workers and their families. Researchers have identified a variety of challenges to estimating chemical exposures including a lack of information on how chemical exposures have changed in particular industries, including changes in practices after a health hazard has been identified (Boffetta, Kogevinas, Simonato, Wilbourn, & Saracci, 1995).

Characterization of Chemical Exposure by Job Task

This may be one of the most neglected areas of occupational cancer research. Risk can no longer be characterized by reliance on broad job categories alone. Instead, occupations must be characterized by specific tasks, especially those in which chemical exposures are more likely. Understanding the variation in exposure intensity to a chemical within a job task is also needed (Kennedy & Koehoorn, 2003; Messing et al., 2003).

Determining Whether Gender Differences Affect the Magnitude of Exposures

Gender differences may affect the magnitude of chemical exposures in women, and hence cancer risk. The higher percentage of body fat, smaller water volume, lung volume, and body surface area, and thinner skin of women have been hypothesized to result in higher exposures than among men for the same job task (Blair et al., 1999; Greenberg & Dement, 1994; Kennedy & Koehoorn, 2003; Messing et al., 2003; Pottern et al., 1994), but few studies have actually tested this hypothesis.

Using Molecular Approaches to Identify Gene–Environment Interactions

Certain metabolic pathways responsible for the activation of carcinogens in the liver are the same pathways used in the synthesis and degradation of female hormones such as estrogen. These include enzymes in the cytochrome P450 metabolic pathways. Non-occupational studies have begun to evaluate whether women with variants in the genes (polymorphisms) controlling these important enzymes may have a higher breast cancer risk. To date, these molecular approaches to evaluating gene–environment interactions have not been commonly extended to identifying at-risk subpopulations in occupational settings. Although women with a first-degree relative with breast cancer have a higher risk, it is not known whether this is the result of shared genes, a shared environment, or an interaction. The long-term, prospective Sister Study, sponsored by the National Institute for Environmental Health Sciences, consists of 50,000 women whose sisters have been diagnosed with breast cancer. It will store and analyze cheek cells from swish and spit samples to identify genes related to breast cancer risk. The researchers will also monitor levels of environmental chemicals in blood, urine, and toenail samples and obtain detailed diet, lifestyle, and occupational history data. More information on the Sister Study is available at www.sisterstudy.org.

CONCLUSIONS

Established risk factors explain only 25% to 50% of breast cancer cases, hence the interest in the role of environmental factors. Although the number of women in the work force has increased dramatically since 1950, most occupational cancer studies have involved men. Occupational cancer risks need to be evaluated in women because certain cancers can only be studied in women, men and women have distinct biological differences affecting exposure, and some new industries primarily employ women. Exposure to organic solvents, metals, acid mists, ethylene oxide, some pesticides, light at night, and tobacco smoke has resulted in increased mortality or breast cancer incidence among women in occupational settings. A variety of occupations have been identified as having a higher breast cancer risk, but specific exposures to suspect chemicals often have not been determined. Types of research needed to better identify breast cancer risks in occupational settings include monitoring cancer risk in occupations with exposures to suspected carcinogens, characterizing chemical exposures by job type and task, determining whether potential gender differences affect chemical exposures, and using molecular approaches to identify gene–environment interactions.

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IN SUMMARY

Chemical Exposures in the Workplace

Effect on Breast Cancer Risk Among Women

Snedeker, S. M.

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1 Occupational health nurses need to be aware of the current science on breast cancer risks in the workplace because they are risk communicators for employees and their families. Occupational health nurses can serve as advocates for necessary research ultimately leading to risk reduction and prevention strategies in the workplace.

2 Current research suggests exposure to organic solvents, metals, acid mists, sterilizing agents (ethylene oxide), some pesticides, light at night (shift work), and tobacco smoke increases breast cancer risk among women in occupational settings. Animal cancer bioassays conducted by the National Toxicology Program indicate more than 40 chemicals can induce mammary tumors, and most of these are still in production.

3 A variety of occupations worldwide, including health care providers and metal, textile, dye, rubber, and plastic manufacturing workers, have been identified as having some evidence of higher breast cancer risk. Although some chemical exposures are suspected to affect breast cancer risk, estimates of or actual exposures to these chemicals in the workplace often have not been determined.

4 Research needed to better identify breast cancer risks in occupational settings includes monitoring breast cancer incidence in occupations with exposures to suspected carcinogens, characterizing chemical exposures by job type and task, determining whether potential gender differences affect chemical exposures, and using molecular approaches to identify gene–environment interactions.

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CE Answers

The Energy Employees Occupational Illness Compensation Program Act: New Legislation to Compensate Affected Employees

June 2005

1.	B	6.	B
2.	D	7.	A
3.	C	8.	B
4.	C	9.	D
5.	A	10.	B