Occupational Cancer Among Women: Research Status and Methodologic Considerations

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Occupational causes of cancer have not been well-evaluated among women. An increase in the number of women in the work force in jobs with potentially hazardous exposures during the past few decades raises the question as to whether there is a need to enhance our efforts in this area. The inability to evaluate occupational causes of female gynecologic tumors in studies of men, plus the potential for variation in outcome responses between men and women because of gender-based exposure and susceptibility differences, underscore the need for investigations specifically focused on women. Investigations of occupational exposures and cancer risk among women may require design considerations that differ somewhat from studies of men. Issues to consider include the impact of studying outcomes with high survival (e.g., breast cancer), gender-specific exposure patterns and toxicokinetic processing of some chemicals, special limitations in the use of the general population as the referent, and the need to control for established risk factors for gynecologic tumors. Am. J. Ind. Med. 36:6–17, 1999. *Published 1999 Wiley-Liss, Inc.*†

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BACKGROUND

Despite several early historical examples of a relationship between occupation and cancer among women (e.g., breast cancer among nuns [Ramazzini, 1700], lung cancer among workers engaged in the production and purification of radium [Hunter, 1976], and bone cancer among radium dial painters [Martland and Humphries, 1929]), in recent decades research on occupational exposures has focused predominantly on men [Zahm et al., 1994]. The limited effort regarding occupational studies of cancer among women is probably a reflection of the tendency for women in past years to hold jobs in service occupations with different and lower exposures to potential carcinogens than occupations in manufacturing and heavy industry. Although a recent tally of articles on occupational disease suggests some improvement in inclusion of women, this upturn is less evident for studies of occupational cancer than other outcomes [Greenburg and Dement, 1994]. Hopefully, this International Conference on Women's Health: Occupation, Cancer and Reproduction, and the earlier conference held about 5 years ago, will stimulate health research among working women and ultimately lead to identification and control of workplace hazards for all workers.

WHAT IS KNOWN REGARDING OCCUPATIONAL CANCER AMONG WOMEN?

Occupational associations with selected cancers among women have recently been reviewed [Zahm et al., in press], and associations between occupational exposures and selected cancers were noted.

Several studies have evaluated the relationship between occupational exposures and leukemia. Benzene is a well-established carcinogen [IARC, 1987] and an excess of leukemia has been observed among exposed women, as well as men [Li et al., 1994]. Leukemia has also been reported among women potentially exposed to other solvents while employed as chemists, engineers, and laboratory workers

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[Bulbulyan et al., 1992; Walrath et al., 1985; Burnett and Dosemeci, 1994; Morton and Marjanovic, 1984], dry cleaners [Morton and Marjanovic, 1984], and beauticians [Giles et al., 1984]. Leukemia has been reported to be elevated among women employed in health care professions [Linet et al., 1994; Skov et al., 1992; Bulbulyan et al., 1992; Burnett and Dosemeci, 1994; Morton and Marjanovic, 1984; Lynge, 1994], oncologic nurses [Skov et al., 1992; Lynge, 1994], clinical laboratory technicians [Burnett and Dosemeci, 1994], and diagnostic X-ray workers [Wang et al., 1988]. Leukemia has also been noted among women in agriculture [Linet et al., 1994; Blair et al., 1993; Ronco et al., 1992; Giles et al., 1984] and the textile and apparel industries [Linet et al., 1994; Stayner et al., 1985; Aronson and Howe, 1994].

Lung cancer is a well-established occupational cancer [Blot and Fraumeni, 1996] and it has been observed among women with potential exposure to asbestos through jobs in assembly of gas masks and textiles [Wignall and Fox, 1982; Acheson et al., 1982; Newhouse et al., 1985; Dement et al., 1994; Newhouse et al., 1972; Botta et al., 1991; Brownson et al., 1993; Rosler et al., 1994], construction [Carpenter and Roman, 1995; Gunnarsdottir and Rafnsson, 1992, 1995; Rubin et al., 1994; Robinson et al., 1995; Wu-Williams et al., 1993; Robinson and Burnett, 1994], and other ways [Spirtas et al., 1994]. Excesses of lung cancer occurred among women exposed to polycyclic aromatic hydrocarbons and oils in metal working [Blot and Fraumeni, 1996], metal working and grinding [Carpenter and Roman, 1995; Rubin et al., 1994; Wu-Williams et al., 1990, 1993; Lubin and Blot, 1984; Park et al., 1988; Hogan et al., 1990; Olsen and Jensen, 1987], and motor vehicle assembly [Delzell et al., 1994; Aronson and Howe, 1994; Wu-Williams et al., 1993; Beall et al., 1995; Wang et al., 1995]. Women employed in the fur hat industry with possible exposure to mercury had a reported excess of lung cancer in one study [Merler et al., 1994]. Tobacco smoke and polycyclic aromatic hydrocarbons may account for the excesses of lung cancer observed among waitresses, bartenders, and cooks [Carpenter and Roman, 1995; Bulbulyan et al., 1992; Rubin et al., 1994; Dimich-Ward et al., 1988; Kjaerheim and Andersen, 1994; Mench et al., 1977; Lubin and Blot, 1984; Olsen and Jensen, 1987].

A number of occupational exposures are known to cause bladder cancer among men and most of these are also risk factors among women [Silverman et al., 1996]. Occupations held by women where excesses of bladder cancer have been reported include textile workers with possible exposure to dyes [Carpenter and Roman, 1995; Silverman et al., 1990; Delzell and Grufferman, 1983; Xue-Yun et al., 1990; Bulbulyan et al., 1995; Gonzalez et al., 1989; Cordier et al., 1993; Maffi and Vineis, 1986], rubber and plastics workers [Swanson and Burns, 1997; Carpenter and Roman, 1995; Silverman et al., 1990; Solionova and Smulevich, 1993], leather workers [Garabrant and Wegman, 1984; Decoufle, 1979], and painters [Silverman et al., 1989b]. Bladder cancer excesses have also been reported among women employed in dry cleaning [Blair et al., 1990; Ruder et al., 1994; Katz and Jowett, 1981], health care [Carpenter and Roman, 1995; Silverman et al., 1989], miscellaneous manufacturing jobs [Swanson and Burns, 1997; Carpenter and Roman, 1995; Silverman et al., 1990; Olsen and Jensen, 1987], and as gardeners [Silverman et al., 1989b], teachers [Rosenman, 1994], waitresses [Silverman et al., 1989b], maids [Davis and Martin, 1988], seafarers [Pukkala and Saarni, 1996], and telephone operators [Dosemeci and Blair, 1994].

Only a few studies are available on occupational factors and brain cancer among women, but increased risks have been reported among women employed in the electronics industry and other jobs with possible electromagnetic field exposure [Fear et al., 1996; Park et al., 1990; Heineman et al., 1995; Ryan et al., 1992], textiles [Heineman et al., 1995; McLaughlin et al., 1987], construction [McLaughlin et al., 1987], teaching [King et al., 1994; Rosenman, 1994], telephone industry [Dosemeci and Blair, 1994], and farming [Heineman et al., 1995].

An early occupational link with breast cancer was the high rates among nuns [Ramazzini, 1700], now known to be due to reproductive patterns. Other occupational groups that may have high rates of breast cancer that may be due, in part, to reproductive history include professional and technical workers such as teachers, chemists, physicians, and nurses [Zahm, in press]. Labreche and Goldberg [1997] postulate a role for organic solvents in the development of breast cancer because they cause mammary cancer in laboratory animals and accumulate in the breast. Excesses for breast cancer have also been reported for women employed in the chemical industry [Morton, 1995; O'Berg et al., 1987; Hall and Rosenman, 1991; Cantor et al., 1995], drug manufacturing [Hall and Rosenman, 1991; Thomas and Decoufle, 1979; Hansen et al., 1994], and cosmetology [Morton, 1995; Teta et al., 1984; Hogan et al., 1990; Pukkala et al., 1992].

Ovarian cancer has not traditionally been considered to have occupational determinates. However, women engaged in the assembly of gas masks during World War II had excesses that increased with intensity and duration of exposure to asbestos [Wignall and Fox, 1982; Acheson et al., 1982; Newhouse et al., 1985; Edelman, 1992].

WHY STUDY OCCUPATIONAL EXPOSURES AMONG WOMEN?

Investigations of occupational exposures among men or women have been invaluable in identifying environmental carcinogens. There are, however, a number of associations between cancer and specific occupations for which the evidence regarding carcinogenicity is not clear and where

TABLE I. Suspected Associations Between Occupations and Cancer for Which Specific Agents Have Not Been Clearly Identified*

Occupational group	Cancer sites
Agricultural workers	Leukemia, lip, liver, lung, non-Hodgkin's lymphoma, testis
Architects	Kidney
Artists	Bladder, prostate
Bakers	Lung
Brewery workers	Various sites
Cement workers	Lung, stomach
Chemists, chemical workers	Brain, breast, cervix, genitourinary, colon, lung, lymphatic and hematopoietic, ovary, skin, testis
Coal miners	Leukemia, lung, stomach
Dry cleaners	Bladder, cervix, kidney, liver, lung
Firefighters	Various sites
Leather workers	Bladder
Meat workers	Hodgkin's disease, lung
Oil refinery/petrochemical workers	Leukemia, bone, brain, kidney, lymphoma, pancreas, skin
Paint manufacturers	Bladder, kidney, liver, lung, myeloma
Pattern makers	Colon
Pesticide-exposed workers	Lymphatic and hematopoietic, skin, lung
Plumbers	Lung, lymphatic and hematopoietic
Printing workers	Lung, skin
Pulp and paper workers	Various sites
Rubber industry workers	Bladder, leukemia, lung, skin, stomach
Steel makers	Lung
Truck drivers	Lung, bladder
Veterinarians	Leukemia
Waiters	Lung
Welders	Lung

*Modified from Monson [1996].

the specific agent(s) have not been identified [Monson, 1996]. Several of these occupations include sizable numbers of women, including agricultural workers, architects, artists, bakers, chemists, dry cleaning workers, hairdressers, textile workers, and waitresses (Table I). Additional investigations are needed to clarify cancer risks among persons in these occupations and women should be included.

For many occupational exposures, there is already information regarding cancer risks among men. When such information is available is there any need to also have studies among women? Increasing employment in industries where they were largely excluded in the past is often used as a need for studies on women. It is clear that over the past few decades employment patterns for women have changed dramatically [Stellman, 1994]. Zahm et al. [in press] note that where only 34% of women were employed outside the home in 1950, this had risen to 59% in 1994 and that this

TABLE II. Why Studies of Occupational Cancer Among Women Are Needed

Item	Issue
Breast and gynecologic tumors	Some cancers can only be investigated in women
Gender-specific responses	Site and histologic type may vary by sex
Carcinogen potency	Susceptibility and level of risk may vary by sex
Exposures	Exposure patterns and levels may be gender-specific

increase is also accompanied by changes in types of jobs held. For example, the proportion of mechanics and repairers who are women has tripled over this 40-year period. These changes do not, by themselves, provide sufficient justification for gender-specific investigations. The critical issue is whether results from investigations on men are relevant and sufficient to characterize risks among women. It seems reasonable to assume that substances that cause cancer in men would be carcinogenic in women and there are numerous examples to demonstrate this. Although in most situations, studies on men would be expected to provide important and relevant information regarding disease risks among women, there are several reasons why we should not rely entirely upon data from one gender (Table II).

Breast and Gynecologic Tumors

First, gynecologic tumors cannot be studied in men. Second, investigations of breast cancer in men, although not impossible, are of questionable relevance to women and suffer from small numbers. Occupational or environmental exposures have not traditionally been considered to be of much importance in the development of breast and gynecologic cancers and they have rarely received much attention in investigations or in reviews of these tumors. While it is clear that the major risk factors known to date are hormonal [Henderson et al., 1996; Kelsey et al., 1994], there has been a growing interest in various nonhormonal factors, fueled to a considerable extent by the concern over xenoestrogens [Davis et al., 1993]. Recent reviewers of the epidemiologic literature recommend that occupational and environmental exposures receive greater attention in the future, particularly in regard to chemicals with hormonal properties, organic solvents, and pesticides [Zahm et al., in press; Goldberg and Labreche, 1996].

Experimental data support the hypothesis that occupational and environmental exposures may play a role in the development of breast and gynecologic tumors. Some chemicals cause ovarian or uterine cancers in animal bioassays (e.g., benzene, butadiene, bromoethane, ethylene oxide) and several cause mammary tumors (e.g., acrylonitrile, benzene, butadiene, dibromoethane, dichloroethane, sulfallate, and trichloropropane) [Griesemer and Eustis, 1994]. Since both epidemiologic and experimental data indicate a possible role for occupational exposures in the development of breast and gynecologic cancer, it is clear that investigations of women focusing on occupational exposures are clearly needed.

Gender-Specific Responses

The correlations between the sexes regarding the carcinogenicity of chemicals in experimental animals is quite high, e.g., nearly 90% [Huff et al., 1991]. There are situations, however, where the type of cancer produced by a carcinogen may differ between males and females. The variation in gender-specific background rates for several tumors differ in rodents and provides indirect evidence for differences by sex [Griesemer and Eustis, 1994]. Liver cancer is about twice as common among males as females in rats and mice, while cancer of the pituitary gland is twice as common among female rats and 50 times more frequent in female mice. Gender differences among rodents are not likely to be due to different external exposures and are more likely to represent fundamental biologic dissimilarities between males and females than in humans, where gender-related exposure differences may also be a factor.

Animal bioassays provide direct evidence for exposure-related gender differences (Table III). Bromoethane causes lung adenomas in male mice and cancer of the endometrium in females, as well as brain and adrenal gland cancers in male rats and cancer of the mammary glands in female rats. Chloroethane causes lung cancer in male mice, but hepatocellular and uterine cancers in females. It causes skin cancer in male rats and astrocytomas in females. Butadiene causes hemangiosarcomas, lymphomas, and cancer of the lung and forestomach in male and female mice; but in addition, it causes liver, mammary, and ovary cancers in females. These findings indicate that sex-specific responses occur for tumors other than reproductive organs and suggest that human data based primarily on studies of one sex would be incomplete.

TABLE III. Tumors From Selected Chemicals by Gender in Bioassays

Chemical	Species	Males	Females
Bromoethane	Mice	Lung adenomas	Uterine endometrium
	Rats	Adrenal gland	Mammary gland
		Brain	
Butadiene	Mice	Hemangiosarcomas	Hemangiosarcomas
		Lymphomas	Lymphomas
		Lung	Lung
		Forestomach	Forestomach
			Liver
			Mammary gland
			Ovary
Captan	Mice	Duodenal	
	Rats	Forestomach	Mammary gland
Chloroethane	Mice	Lung	Uterine
			Hepatocellular
	Rats	Skin	Astrocytomas
Ethylene oxide	Rats	Brain	Brain
		Leukemia	Leukemia
		Mesothelioma	
Sulfallate	Mice	Lung	Lung
			Mammary gland
	Rats	Forestomach	Mammary gland

We are not aware of any human data that clearly demonstrate that an established carcinogen causes different nonreproductive cancers in men and women. For most occupational carcinogens, however, we are handicapped by the limited number of investigations and small number of women who have been studied. Some information on this issue may be gleaned from studies of tobacco, where, although the cancer sites are the same for men and women, there appears to be differences in histologic types of lung cancer. Tobacco is a powerful lung carcinogen in men and women. Adenocarcinoma is more common among women smokers, while squamous cell is the more common histologic type among men [Bianchi et al., 1997]. This difference in cell type may simply reflect some basic gender difference for lung cancer, since among nonsmokers squamous cell lung cancer also predominates among men, while adenocarcinomas are more common among women [Anton-Culver et al., 1988; Ernster, 1996], regardless of the amount and type of tobacco use. One wonders that if such histologic differences persist with smoking, perhaps it is not unreasonable to suspect that similar differences might also occur with occupational and environmental exposures.

Gender-exposure interactions may also introduce differences in risk between men and women. Taioli and Wynder [1994] suggest that estrogen may have an impact on the development of lung cancer in women. They base this on an interaction they observed between use of replacement estrogens and smoking on the risk of lung cancer. The authors speculated that use of estrogens might influence the carcinogenic process at the promotional stage.

Gender Differences in Carcinogen Potency

Some epidemiologic data suggest that the potency of certain carcinogens may vary by gender. Several investigators have reported a greater risk of lung cancer among women from tobacco use than men, even after standardizing level of use [Brownson, 1992; Risch et al., 1993; Engeland et al., 1996; Zang and Wynder, 1996; Baldini and Strauss, 1997; Tulinius et al., 1997]. Prescott et al. [1997], however, found no such effect. A number of explanations for these observations are possible. The higher relative risks among women may simply be due to chance findings because the gender difference is neither large nor consistent across studies. It could also be an artifact caused by the impact of a constant absolute increase in risk on different background rates. A differential impact could arise if smoking caused the same absolute increase in risk of lung cancer among men and women. In such a situation, the higher baseline rate among men would translate into a lower relative risk for men compared to that for women. On the other hand, these data may indicate a greater susceptibility of women to tobacco carcinogens than men. If true for tobacco, a similar gender difference may operate for other carcinogens as well, which implies that data on women would be essential for a full understanding of societal risks and for decision-making on public health policy.

Epidemiologic data are typically insufficient to compare cancer risks from occupational exposures by gender. Two factors complicate such a comparison. First, studies of well-established carcinogens seldom include enough women to provide stable estimates of their cancer risks. Second, gender comparisons are often complicated by level of exposure. We have not made a thorough survey of the literature on this issue, but a few examples might be illustrative.

A study of workers engaged in maintenance and repair of aircraft suggested that women may experience greater risks of multiple myeloma and non-Hodgkin's lymphoma than men from exposure to solvents and other chemicals [Blair et al., 1998a]. The differences in relative risks were not statistically significant and the number of deaths among women for specific exposures was typically small. The relative risks for women, however, were consistently larger than among men. Relative risks for women ranged from 2 to 5, while those for men were less than 3. In a case-control study, relative risks for mesothelioma from asbestos exposure were considerably larger among men (OR = 9.8) than among women (OR = 1.8) [Spirtas et al., 1994]. This difference is thought to be due to lower exposure levels among women. Occupational exposures and multiple myeloma have been studied among men [Heineman et al., 1992] and women [Pottern et al., 1992] in Denmark. Although no striking excesses occurred for either gender, a job-exposure matrix showed slighter larger relative risks among women than men from exposure to engine exhausts (1.4 vs. 1.3), wood dust (1.8 vs. 1.2) and leather dust (2.1 vs. 1.4). Comparison of the mortality experience of men and women farmers showed some similarities and some differences [Blair et al., 1993]. Silverman et al. [1989a, 1990] evaluated risk of bladder cancer by occupation in a very large case-control study and found few differences between men and women for a priori suspect occupations. These few examples show no clear pattern, but they may not accurately represent the full literature. A thorough review of the literature regarding cancer site/exposure relative risks among men and women would be informative.

TABLE IV. Factors Affecting Occupational Exposures Among Women

Factor	Implications for research
Gender-based job patterns	Different exposures for men and women
Job task assignments by gender	Different exposures for men and women
Approach to job tasks	Different levels of exposure for men and women
Temporal factors (age at first exposure, duration of exposure)	Duration of latency

Gender Differences in Exposure

Differences in occupational exposures among men and women may occur for several reasons (Table IV). These differences could affect cancer rates and complicate the extrapolation of risks from men to women. In many countries (maybe most), jobs have a distinct gender cast. Men predominate in some jobs; women in others. This is changing somewhat as women move into positions traditionally occupied by men. In the United States, however, many jobs still have a gender predominance. For example, 90% of private household service workers and nurses are women, but women make up only a small proportion of construction workers [Stellman, 1994].

Different levels of exposure between men and women having contact with the same chemicals could also have important implications for gender-specific research because of the effect of exposure level on type of cancer and relative risk. There are several components to gender-based exposure differences within jobs. These include differential assignment of job tasks based on gender, gender-specific approaches to performing the same tasks, and variation in effectiveness of protective equipment and engineering controls. Although little monitoring information is available to directly compare exposure levels among men and women holding the same job, other information suggests that differences might occur. Even if the job title is identical, men and women may not be performing the same type of work. In interviews with workers, Messing et al. [1994] found that a large proportion of men and women felt that tasks within jobs varied by gender. Information and observations on how men and women perform identical job tasks and direct measurement of exposures while performing these tasks would be of considerable value.

TABLE V. Gender-Specific Toxicokinetic Factors That Might Affect Dose*

Toxicokenetic factors	Different delivered dose levels
Greater surface area among men	More exposure among men
Larger lung volume among men	More exposure among men
Thinner skin among women	More exposure among women
Higher % body fat among women	Greater storage of lipid-soluble chemicals
Smaller total water volume among women	Less dilution among women

*From Silvaggio and Mattison [1994].

TABLE VI. Methodologic Issues and Challenges in Occupational Studies of Women

Issue	Design implications
Study size	Large numbers required because of the small proportion of exposed women
Disease classification	Incidence studies needed because of poor ascertainment from death certificates
Exposure assessment	Gender-specific procedures required because of special exposure patterns among women
Confounding	Information needed on confounders because relationships between lifestyle, reproductive, and occupational factors are unclear

The timing, level, and duration of exposures could all impact the time between first exposure and diagnosis of cancer. Many women in developed countries start work after their children reach the school years. This means that, for some, the initial exposures occur at a later age than for men and that duration of exposure during working life is also likely to be short. Later age at first exposure and shorter duration may lengthen the time between first exposure and diagnosis of cancer. Gender differences in level of exposure could also result in gender differences in latency. For example, a recent report noted that the time between first exposure to asbestos and diagnosis of mesothelioma was greater among women than men [Bianchi et al., 1997]. Although the reason for this gender difference in latency is unclear, as noted earlier, the relative risk for mesothelioma is considerably different among men and women and this may reflect level of exposure.

A number of physiologic and toxicokinetic differences between men and women may affect delivered dose [Silvaggio and Mattison, 1994] (Table V). Delivered dose may be greater per unit of external exposure among men because of their larger surface area, which provides more opportunity for dermal absorption. Larger lung volumes among men could have a similar affect on inhalation exposure. On the other hand, women have thinner skin in many areas of the body, which may allow easier penetration. A smaller volume of total body water in women means that the concentration of absorbed chemicals would be greater in women than in men. Finally, a higher percentage of body fat among women may allow a larger proportional storage of lipid-soluble chemicals.

In summary, studies of occupational exposures and cancer among women is valuable for several reasons. Epidemiologic studies are needed to determine the magnitude of risk of established causes, to clarify suspected causes, to identify new hazards, and to understand mechanisms of carcinogenesis [Doll, 1981, 1985]. There is no reason why women should be excluded from studies designed to meet these needs. Several lines of evidence underscore the need, at least in some situations, for studies specifically on women to evaluate the risk of their cancer from occupational exposures. Breast and gynecologic cancer cannot be studied among men, and differences between women and men in both exposures and disease outcomes to the same exposure suggest there may be gender-specific effects.

METHODOLOGIC ISSUES AND CHALLENGES IN STUDIES OF OCCUPATIONAL CANCER AMONG WOMEN

Issues regarding disease classification, susceptibility, latency, cancer type and histology, exposure, and host-exposure interactions may have implications for the design of epidemiologic studies of occupational cancer among women (Table VI).

Study Size

In many countries, studies focusing on specific occupational exposures among women need to be larger than similar studies of men. This is because a smaller proportion of women work outside the home and a larger proportion are employed in white-collar occupations [Zahm et al., in press; BLS, 1995]; thus, fewer women than men are likely to hold the occupations, or have exposures of interest. In 1994, about two-thirds of the employed women in the United States held sales or service jobs, while only about one in ten was in the manufacturing industry. When only one in ten hold manufacturing jobs, even in very large studies the number of women likely to have heavy industry exposures is quite small. In a study with 6,000 cancer cases and 2,000 controls [Swanson and Burns, 1995], the number of occupations with 10 or more cases of lung or bladder cancer was small, i.e., 12 occupations for lung cancer and only one for bladder.

Disease Classification

The cohort mortality design, traditionally used in occupational investigations involving men, may not be as useful for studies of women because mortality is a poor indicator of the force of disease for some important cancers among women. For example, the high survival rate for breast cancer indicates that mortality studies would miss many incidence cases, particularly localized tumors where the 5-year survival is over 90% [Ries et al., 1994]. Use of death certificates for disease diagnosis has practical advantages, but also some limitations [Selikoff, 1992]. Less than adequate agreement between death certificates and hospital records for cancers of the cervix and uterus indicates that reliance on mortality as the outcome measure would introduce considerable misclassification of disease into studies of these tumors [Percy et al., 1981]. Use of death certificates can also introduce classification errors for some nonreproductive cancers and would be a problem in studies of both men and women. It is clear that soft-tissue sarcoma and cancers of the liver and skin cannot be studied well using mortality because of the extremely poor agreement between hospital records and death certificates [Percy et al., 1981]. Only incidence-based studies of these cancers are likely to be accurate. On the other hand, mortality data are quite reliable for some cancers, including stomach, pancreas, lung, and bladder [Percy et al., 1981].

The issue of a mortality versus an incident design is important because accurate diagnosis is a critical factor in all epidemiologic investigations. Misclassification of disease, even if nondifferential in relation to exposure, can obscure a true relationship between outcome and exposure [Checkoway et al., 1989]. Use of mortality as the outcome measure would introduce diagnostic difficulties for some cancers and would tend to bias relative risks toward the null.

Lack of information on cancer histology is another diagnostic issue which could complicate comparison of results from men and women. Problems would occur if some exposures cause gender-specific histologic patterns, as suggested for lung cancer and smoking [Baldini, 1997]. Increased relative risks for a rare histologic type for one sex, but a more common type for the other sex, could result in quite dissimilar relative risks for the cancer site if histology is ignored. In such situations, one might conclude the exposure affects cancer in only one sex, or that the magnitude of effect is considerably different.

For several reasons, we believe that among women incidence-based investigations may be preferable to mortality studies. This has implications for study design. Incidence-based studies can typically be accomplished more easily using the case-control design because case ascertainment is usually hospital-based. However, if nationwide population-based tumor registries are available, incidence-based cohort studies are also possible.

Exposure Assessment

Quantitative exposure assessment may require a special approach for occupational studies of women. In most cohort studies, quantitative assessments are developed by job and all workers holding the same job receive identical exposure assignments. This is reasonable if the tasks performed and the approaches used to perform these tasks are the same for all workers holding that job, but these may not be valid assumptions. For example, Rappaport [1991] provided data that indicate that intra-job variability may be greater than previously recognized. Stewart et al. [1996] discuss the assumptions regarding the job-based approach and problems that occur when the assumption of homogeneity of exposure within a job is false. In general, it introduces nondifferential misclassification. Gender differences in exposure have not received much attention, but they probably do occur and, if widespread, then job-based exposure estimates would need to be gender-specific to address differential assignment of tasks and varying approaches to performing job tasks. We have not used this approach at the National Cancer Institute in retrospective cohort studies of occupation and cancer [Stewart et al., 1986, 1998; Dosemeci et al., 1993, 1994] and we are unaware of any investigators who have.

Direct monitoring would be the most straightforward method of assessing the occurrence of gender-based exposure differences. Unfortunately, few historical monitoring data of any kind are available and we may have to rely on other information to develop gender-specific exposure estimates. Information on gender-specific task assignment would probably require direct contact with each study participant because such information is unlikely to occur in company records. Some information on task assignment might be obtained from senior management and long-term workers, but it is difficult to imagine how anyone but the subject could provide detailed information on how they actually perform their job. Case-control or prospective cohort studies, where it is possible to interview subjects directly, may be better suited for dealing with this problem than the historical cohort design.

Prospective investigations organized within the workplace that include periodic monitoring and collection of exposure-relevant data, as suggested by Dr. Richard Monson at the First International Conference [Zahm and Pottern, 1995], may be another solution. Such an approach coupled with direct interviews with participants to obtain information on an individual's approach to specific job tasks and nonoccupational risk factors, as well as the collection of biologic specimens for evaluation of gender/genetic susceptibility and gene-environment interactions, would be methodologically powerful. Of course, these designs have their own problems, particularly high cost to conduct and lengthy time to complete.

Vital Status Determination

Assessing vital status in retrospective cohort studies may present special problems among women because of the difficulty in tracing. Name change is the most obvious challenge. Ascertainment of vital status in cohort mortality studies is usually less successful for women and minority men than for white men. Results of successful determination of vital studies among white men and white women in studies at the National Cancer Institute were 96% and 83% among formaldehyde workers [Blair et al., 1986], 96% and 90% among furniture workers [Miller et al., 1989], 92% and 88% among dry cleaners [Blair et al., 1990], 99% and 93% among aircraft maintenance workers [Spirtas et al., 1991], and 97% and 92% among acrylonitrile workers [Blair et al., 1998b]. These are small differences but they indicate that more deaths will be missed among women than among men. This is likely to have relatively little impact on relative risks when internal comparisons are made, but the effect could be somewhat larger if the general population is used as the referent. In the latter situation, the estimated relative risk would be diminished.

Confounding

Selection of an appropriate comparison population for occupational studies of women may present special challenges. In occupational studies of men, the general population has often been used. Despite some well-recognized problems, e.g., the healthy worker effect [Checkoway et al., 1989], this has proven to be a reasonably sound and efficient approach. The general population, however, may not be as suitable a referent for studies of women. Most men in the general population are employed — the comparison is to a large extent between individuals employed in a specific occupation or industry and those employed in other occupations or industries. For women, however, a sizable fraction of women in many countries is not employed outside the home. This may lead to confounding if employed women differ from unemployed women with regard to important risk factors for the disease of interest. Factors that may differ between women working outside the home and homemakers include tobacco, alcohol use, and reproductive history.

A number of investigators have evaluated patterns of tobacco use by occupation [Sterling and Weinkam, 1976; Brackbill et al., 1988; Stellman et al., 1988; Levin et al., 1990; Nelson et al., 1994]. Differences in tobacco use by occupation occur among women as well as men. The smoking pattern for women not in the labor force (the category where homemakers would be classified), however, is unclear. Brackbill et al. [1988] report that women not in the labor force have a higher smoking prevalence than employed or unemployed women, while Nelson et al. [1994] found they have a lower prevalence. Consequently, based on these data one cannot confidently predict what effect the use of the general population as the reference in occupational studies of women might have on estimates of relative risk. Because confounding of associations between occupational exposures and risk of cancer is not a common occurrence in men [Blair et al., 1995], it may not be much of a problem among women. We need, however, to develop a better understanding of patterns for established cancer risk factors by occupation among women.

Little information is available regarding the distribution of risk factors for cancer other than smoking across occupations for women. Lower parity has been reported among working women [Kryston et al., 1983]. Working women were more likely to be nulliparous than housewives and had fewer children [Boffetta et al., 1995]. Petralia et al., [1999] found lower parity and older age at first live birth among teachers and nurses than in other occupations. In contrast, Gunnarsdottir and Rafnsson [1995] found that the fertility rate and age at first birth among Icelandic nurses were similar to the general population.

CONCLUSIONS

Cancer risks from occupational exposures have not been well investigated among women. There are several reasons why investigations among men may not fully characterize the situation in women. First, gynecologic tumors cannot be evaluated in men. Second, exposures may differ between men and women holding the same job. Finally, biologic differences by gender may lead to different levels of risk, or different outcomes, even when external exposures are similar.

Although future investigations should do a better job of evaluating risk of occupational cancer among women, we could expand our understanding of occupational risks among women by more complete analyses of data already available. Much too often, studies with information on women present little or no data on their disease risks.

Investigations of occupational exposures and cancer among women may require special design features. Cohort mortality studies may not work well for a number of cancers, including breast and gynecologic, because of diagnostic errors associated with death certificates. Exposure assessment techniques typically employed for cohorts of men may require modification for use on women because of gender differences in the assignment of job tasks and the approaches used to complete these tasks. High quality assessments of historical exposures for women are likely to require direct interviews with study participants, which points toward a preference for case-control and prospective cohort designs. Another disadvantage of retrospective cohort designs is that they are usually assembled from large industrial facilities, and workers from small businesses are seldom included, which may exclude workers with heavier exposures.

RECOMMENDATIONS

Measurements of occupational exposures on women are rare. These are needed to improve the quality of exposure assessment in occupational studies of cancer among women. As among men, high quality exposure assessment is essential for the identification and clarification of occupational carcinogens.

Methodologic investigations on the relationship between established risk factors for female tumors and occupational exposures are needed. Such information would help in the interpretation of studies that lack direct information on potential confounders, e.g., datasets that link census data with mortality or cancer incidence records.

Data on women, occupational exposures and cancer currently available need to be fully analyzed. Studies with small numbers of women relative to the number of men can expand the base and provide direction for future research.

Studies focusing on occupational exposures and cancer among women need to be large. This is because in most developed countries a significant proportion of women have had little employment outside the home. This may require weighted-sampling to increase the number of women holding nonclerical jobs to achieve desired statistical power for specific exposures. Although the proportion of women employed outside the home is rising in most developed countries, investigations in developing countries may offer unique opportunities because a larger proportion of women are employed in nonclerical jobs where exposures are more substantial than is typically found in developed countries. A pooling of epidemiologic expertise from developed and developing countries may provide the opportunity to conduct research that could not be accomplished by either group by itself. Investigators at the National Cancer Institute in the United States, in collaboration with scientists from the country of study, have successfully conducted case-control studies of stomach cancer in Poland, multiple cancers in Turkey [Dosemeci et al., 1997], and are planning a study of breast cancer in Poland. A cohort of 75,000 workers exposed to benzene has been evaluated for cancer in China [Hayes et al., 1997] and a study of 90,000 women in Shanghai has been initiated to investigate dietary and occupational factors in the development of cancer. The experience of the IARC and others also indicate that these can be very productive collaborations.

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