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Occupation and Prostate Cancer

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INTRODUCTION

The descriptive epidemiology of prostate cancer, including international comparisons of incidence, temporal trends, social class gradients, and migrant studies, suggests that incidence varies greatly and that exogenous factors may play an important etiologic role (1, 2). Despite attempts to investigate the roles of several classes of exogenous agents, there are still no definitely recognized exogenous risk factors for prostate cancer.

While there is still limited physiologic evidence on the extent to which different exogenous chemicals may affect the prostate gland, the principle that such chemicals can alter enzymatic activity is established (3, 4). Further, animal experiments have demonstrated that prostate tumors can be induced by administration of certain chemicals by various routes (5). It has been hypothesized, though not yet proven, that such carcinogenic effects may be mediated by hormonal influences. Experimental evidence indicates the possible role of androgens as initiators in prostate carcinogenesis (6, 7), while other studies have shown that estrogens can induce DNA damage (8). Various exogenous chemicals may affect hormone levels, which may, in turn, affect estrogen levels and androgenic stimulation of the prostate (2, 9–11).

In this presentation, we consider evidence regarding the possible role of occupation and occupational exposures. Investigating cancer risks in relation to occupational exposures is important because exposure levels in the workplace may be higher than elsewhere and because most workplace substances find their way into the general environment in one form or another. A thorough review of possible associations between prostate cancer and all occupations and occupational agents would have been beyond the scope of this brief review; instead, we restricted our attention to a handful of occupations and occupational agents which have, in one way or another, already come under particular suspicion and scrutiny. These (partially overlapping) occupations and agents are: farming, pesticides, cadmium, metal working, polycyclic aromatic hydrocarbons, and the rubber industry. Considerable attention has recently been paid to farming, and we will consequently devote particular attention to this occupation. We will not consider occupational physical activity here as it is included elsewhere in this issue of *Epidemiologic Reviews*.

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OCCUPATIONS AND AGENTS UNDER REVIEW

Farmers

Over 60 epidemiologic studies and broad occupational surveys have examined the relation between farming and prostate cancer. Subsets of these studies and surveys have been subjected to three recent meta-analyses (12–14) and to numerous qualitative reviews (9, 12, 15–22). Each of the three meta-analyses reported a slightly increased, statistically significant, summary relative risk in the order of 1.1, consistent with a very weak, positive association. Most recent studies which postdated these meta-analyses also suggest elevated risks among farmers (23–27), although others have found reduced or no excess risks (28, 29). The ostensible slight excess of prostate cancer contrasts with low risks for most other cancers and non-neoplastic diseases among farmers (12). The interpretation of this body of evidence remains uncertain (30). We will consider two questions: Is there a greater risk among farmers? and if yes, what does it tell us about the etiology of prostate cancer, and, in particular, about the "occupational" etiology of prostate cancer?

Is there an association?

With meta relative risks in the order of 1.1 and lower 95 percent confidence limits close to 1.0, chance cannot be excluded as an explanation for this pattern of findings, nor can systematic bias. For instance, since several of the studies were based on proportionate mortality ratios or on the use of controls selected from other cancer series, it is possible that low risks of other diseases among farmers would manifest as an ostensible excess risk of prostate cancer. Further, while the authors of these meta-analyses tried to avoid publication bias, it is difficult to ensure its elimination, and with such a low meta relative risk, it remains possible that selective publication of results can explain the preponderance of positive results (31).

It is not clear whether the nature of the results was differential according to study quality. Retrospective cohort studies tended to have lower relative risk estimates than did routine records, proportionate mortality ratio studies, and case-control studies, and Acquavella et al. (14) implied that this corresponded to a difference in methodological quality. On

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the other hand, it does not appear that recent studies, perhaps using more sophisticated methods, gave lower estimates than earlier studies (13).

Many of the studies examining prostate cancer in farmers were the hypothesis-generating type, consisting of linkages of large existing databases. Prostate cancer status was most often ascertained from death certificates. Since prostate cancer is not invariably fatal, and since death certificates are error-prone, the body of evidence from such sources has an element of error. However, even among studies based on incident cases, a preponderance show excess risks among farmers and farm laborers (21).

One source of downward bias could have been misclassification in designating subjects as farmers based on scant and unreliable information on death certificates.

In summary, it cannot be affirmed with confidence that farmers experience excess risks of prostate cancer, but the evidence leans in that direction.

Meaning of an increased risk if there is one

Lifestyle. More than any other occupation group, the designation of "farmer" signifies much more than what we conventionally think of as an occupation. Farming entails a way of life that is so different from that of most non-farmers that it is difficult to separate out the components that belong in the "occupation" cubby-hole from those that belong in the "lifestyle" cubby-hole. The reader will have noticed that, in considering the question of whether the association is real, we did not even consider confounding by lifestyle as an issue. The lifestyle and the job are inextricably linked. But in considering to what one might attribute an excess risk of prostate cancer among farmers, it is certainly relevant to consider lifestyle issues.

Compared with non-farmers, Iowa farmers smoke less, use less alcohol, have less formal education, and consume more total calories from fat, protein, and meat while consuming fewer calories from fruits and vegetables (32). The same patterns have been observed elsewhere regarding smoking and alcohol, at least (33–35). There are self-evident differences in source of drinking water, diurnal sleeping patterns, sunlight exposure, amount of physical activity, and exposure to urban noise and pollution. There may be differences in psychosocial characteristics and sexual habits. Although there are no clearly established environmental/lifestyle risk factors for prostate cancer, some of the above are suspected (36–38). The eating habits of farmers have come under some scrutiny since there is increasing evidence that fat consumption and/or chemical contaminants in fat, notably organochlorines from pesticides and herbicides, may increase production and bioavailability, or mimic the action, of androgenic hormones (11). Since farmers apparently consume more fat, they might have greater exposure to dietary fat contaminants than non-farmers. Whether these or other lifestyle factors can explain the ostensible small excess risk among farmers is speculative. In one recent case-control study (23), adjustment for some of these factors did not attenuate the observed association between farming and prostate cancer, but this was only one small study. The observation that European studies have not shown excess risks among farmers, whereas North American studies have (14), if real, may reflect lifestyle differences or differences in farming practices between countries.

Occupational exposures. In most studies of farmers, the epidemiologic analyses were based on job title designations that covered a great variety of occupational circumstances. In some, it extended even further to include different non-urban occupations such as forestry workers or horticulturists. Rarely have studies differentiated between crop and livestock farming. The category of farmers and farm workers, as designated in most epidemiologic studies, experienced an enormous variety of working exposures. One corollary of this observation is that if there really is a slight excess risk for the entire category, and if this excess risk is not due to lifestyle factors, then there must be much higher relative risks in some sub-groups of farmers.

Farmers' activities encompass a wide variety of tasks including equipment operation, mechanical repairs and maintenance of machinery, soldering, carpentry, pesticide application, and livestock handling (15). Exposures can involve solvents, fuels and oils, metal dusts, welding fumes, engine exhaust, paints, various organic and inorganic dusts, pesticides, herbicides, insecticides, zoonotic viruses, microbes, fungi, and sunlight.

Only a handful of studies have attempted to assess risks in relation to specific exposures among farmers and agricultural workers. Perhaps the best attempt was that of Morrison et al. (39) who were able to use Canadian census databases to assemble a large cohort of farmers and characterize them according to a host of farming practices. They were also able to link the cohort to mortality files and thereby estimate risk in relation to various indices of farming exposures. Of about a dozen indices examined, they detected elevated risks only in relation to use of herbicides. But there are few other studies of farmers which elucidate risks in relation to farm exposures. Thus, for most chemicals to which farmers may be exposed, there is no specific information linking them to risks of prostate cancer. Only for pesticides and herbicides is there a substantial body of evidence, and since evidence regarding carcinogenicity of these agents comes from studies of non-farmers as well as farmers, we will consider this issue separately.

Pesticides and herbicides

Morrison et al. (39) reported excess risks of prostate cancer in relation to herbicides, but not insecticides. Elsewhere, use of pesticides among farmers has been associated with prostate cancer in some (40, 41) but not in all (35, 42) studies. However, there are large numbers of different pesticides, and most of these studies were unable to identify and analyze specific compounds.

Evidence concerning hazards due to pesticides also comes from studies of workers involved in manufacturing or spraying of these compounds. Some studies found excess risks among pesticide manufacturers (43–46) but others did not (47–50). Likewise, among pesticide applicators, the evi-

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dence is conflicting, with some studies indicating excess risks (9, 51–55) and others indicating no excess in risk (56–61). Most of these studies were quite small.

Finally, elevated risks have been reported for workers exposed to fertilizers in a few studies (62, 63) but not in all (39, 41, 64).

Several pesticides and herbicides are organochlorines. It has been hypothesized, though not yet proven, that certain organochlorine and other estrogen-like compounds can induce adverse effects through modulation of various complex biochemical and physiologic pathways (11).

Cadmium

Cadmium can be found in some insecticides and fertilizers, and exposure can occur in several workplaces such as those of smelters, nickel-cadmium battery operations, mines, metal construction sites, and rubber production. Other sources include diet and tobacco smoke (24). Following some early epidemiologic reports of excess risk of prostate cancer among cadmium-exposed workers, mainly in battery production or smelting operations, more recent and larger studies failed to confirm those early reports (65). The cumulative epidemiologic evidence does not support the hypothesis (65, 66).

However, apart from the equivocal epidemiologic evidence, there are other reasons to continue to pay attention to cadmium as a possible risk factor. First, prostatic tumors have been induced experimentally in rodents by oral exposure to cadmium (5, 67, 68). Those experiments illustrated that the carcinogenic effects were hormone-mediated. Indeed, accumulation, retention of cadmium in the prostate, as well as induction of prostatic cancer by cadmium were found to be androgen-dependent. Finally, it has been shown that cadmium can impair cell-mediated immunity, phagocytosis, and natural killer cell activity (69), though the implication of this for prostate cancer etiology in particular is unclear.

Metal workers and related exposures

Van der Gulden (70) reviewed evidence regarding prostate cancer risk in 53 studies covering various types of metal workers, and in 27 studies of mechanics, repairmen, and machine operators. Most of these studies showed slightly increased risks, as have a couple of more recent ones (71, 72). These groups of study subjects experienced a great variety of complex exposure profiles. However, few studies delved into specific exposures. Among those that did, there was some evidence of associations with some metallic dusts and with metalworking fluids such as solvents, cutting oils, mineral oils, heating oils, hydraulic fluids, lubricating oils, and acids (70, 73, 74). However, another group which reviewed the available evidence on the risks of prostate cancer among workers exposed to metalworking fluids considered it equivocal (75).

Polycyclic aromatic hydrocarbons and engine emissions

In two recent studies focusing on prostate cancer and looking at a wide range of occupations and industries, it was observed that positive associations emerged for several occupational circumstances entailing potential exposure to polycyclic aromatic hydrocarbons (27, 28). Although the available evidence is not entirely concordant and no systematic review has been conducted, there is some indication of excess risks in occupation groups with potential exposure to polycyclic aromatic hydrocarbons. These groups include firefighters (27, 28, 76–78), power plant operators (27, 28), foundry workers (24), coke oven workers (79), furnace, kiln, and oven operators (28), chimney sweeps (80), railway workers (24, 27, 28, 74), heavy equipment operators (27), farm machine operators, and paving and stone cutting workers (24). In studies which entailed exposure assessment protocols, Aronson et al. (74) found excess risk in relation to liquid fuel combustion products and polycyclic aromatic hydrocarbons as a class, and Seidler (81) found excess risk in relation to diesel fuel and fumes, soot, tar, and pitch.

It has been reported that diesel engine emissions induce changes in enzymatic activities in the prostate glands of animals (4, 81). In addition, the antiestrogenic effects of certain hydrocarbons, such as benzo(*a*)pyrene, may promote the growth of prostate cancer cells.

Rubber workers

The prostate cancer experience of workers in the rubber industry has recently been reviewed (82, 83). Neither of these reviews found persuasive evidence of an association.

Other exposures

Perhaps the most detailed exposure assessment in relation to prostate cancer comes from the case-control study carried out by Aronson et al. (74). In addition to the results from that study reported above, there were also indications of possible excess risk in relation to the following exposures: formaldehyde, chloroform, and the class of alkanes (C_{18+}). These were in the context of a wide-ranging hypothesis-generating study and would require some confirmation elsewhere.

DISCUSSION

Our review focused on a few occupational circumstances and we relied on previous reviews wherever possible. There is no occupation or occupational agent for which there is persuasive evidence of an association. There seems to be a slightly increased risk among farmers, but that observation is too equivocal and too nonspecific to point to particular etiologic agents. It is plausible that certain pesticides or herbicides, acting as hormone modifiers, may influence prostate cancer risk, but this hypothesis remains speculative. Cadmium was considered as a possible risk factor for several years; at present, the epidemiologic evidence does not support such a hypothesis. However, experimental evidence of cadmium carcinogenicity warrants further attention to possible human carcinogenic effects. Despite the lack of systematic reviews, there is suggestive epidemiologic evidence that prostate cancer risk is increased among workers in metalworking

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operations and among workers exposed to polycyclic aromatic hydrocarbons.

FUTURE RESEARCH

Our inability to affirm with confidence that certain occupational circumstances cause prostate cancer, or to reassure workers that prostate cancer is not a result of workplace exposures, calls out for more research. Understanding whether occupational chemicals cause prostate cancer is important, not only for occupational health implications, but it can give us a crucial understanding of the process of prostate carcinogenesis. Should future research focus on the restricted set of circumstances we presented in this review, or should it be broader, allowing for multiple occupations or exposures to be assessed? We believe it is warranted to follow up the leads already available and to carry out "hypothesis-generating"-type research as well. Among the former, the study of farmers and their exposures should be of top priority, with studies of metalworking occupations as the second priority.

The main limitation of previous research is that the majority of studies relied on job or industry titles or very crude exposure assessment schemes. Even if there were true causal associations between these or other occupational agents and prostate cancer, the vast majority of studies carried out would have been hard-pressed to detect the risks. The marginal benefit of further studies based on job or industry titles alone is quite low. Future studies need to be based on more refined exposure assessment protocols. These can involve information from the subjects themselves, industrial hygiene-based exposure assessment (e.g., based on measurements, or at least on expert opinion), biomarker-based exposure assessment, or combinations of these.

There are many forms such studies can take. Aronson et al. (74) have shown how exposure assessment based on experts, in the context of a population-based case-control study, can lead to informative estimates of risk in relation to scores of workplace exposures. Morrison et al. (39) have shown how record linkage of unique databases can provide valuable estimates of risk in relation to farming and farm exposures. de Jong et al. (49) have shown, in the context of an individual cohort study, what can be inferred with good local industrial hygiene information. Unfortunately, we have no strong examples yet of the potential benefit of incorporating biomarker-based exposure assessment; this remains a challenge in all environmental cancer research.

In the past there has tended to be a tradeoff between study quality and study size. It will be of little value to engage in studies with refined exposure assessment but poor study precision. We need studies that are both good in quality and large in size.

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