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Farming and Risk for Prostate Cancer: Results from a Pilot Case-control Study

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Bachelor of Medicine

China Three Gorges University

2014

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Abstract

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Prostate cancer is the most frequently diagnosed major cancer in men across the world. It has been hypothesized that farmers may be of higher risk for prostate cancer because of their various occupation-related exposures; however, epidemiologic findings regarding this have been inconsistent. To investigate an association of farming with prostate cancer risk, we analyzed data from a previously conducted, community-based case-control study with 113 newly diagnosed incident prostate cancer cases and 258 age and race frequency-matched controls in the Piedmont Triad area of North Carolina from 1994 to 1996. All participants were interviewed, completed questionnaires, and provided blood and urine samples at a study visit. Visits for cases were within two weeks of diagnosis and prior to initiation of any treatment. The estimated adjusted odds ratio (OR) for the farmer-prostate cancer association was 1.63 (95% confidence interval [CI] 0.97 - 2.73), for advanced prostate cancer it was 4.77 (95% CI 1.56 - 14.58), and for those less than 67 years of age it was 2.69 (95% CI 1.24 - 5.84). The findings from this pilot study suggest that farmers may be at higher risk for prostate cancer, perhaps especially for more advanced or aggressive disease.

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I. Abstract

Prostate cancer is the most frequently diagnosed major cancer in men across the world. It has been hypothesized that farmers may be of higher risk for prostate cancer because of their various occupation-related exposures; however, epidemiologic findings regarding this have been inconsistent. To investigate an association of farming with prostate cancer risk, we analyzed data from a previously conducted, community-based case-control study with 113 newly diagnosed incident prostate cancer cases and 258 age and race frequency-matched controls in the Piedmont Triad area of North Carolina from 1994 to 1996. All participants were interviewed, completed questionnaires, and provided blood and urine samples at a study visit. Visits for cases were within two weeks of diagnosis and prior to initiation of any treatment. The estimated adjusted odds ratio (OR) for the farmer-prostate cancer association was 1.63 (95% confidence interval [CI] 0.97 - 2.73), for advanced prostate cancer it was 4.77 (95% CI 1.56 - 14.58), and for those less than 67 years of age it was 2.69 (95% CI 1.24 - 5.84). The findings from this pilot study suggest that farmers may be at higher risk for prostate cancer, perhaps especially for more advanced or aggressive disease.

II. Chapter I -- Background

A. Descriptive epidemiology

Prostate cancer, the most common non-skin malignancy affecting men in the United States, is also the most frequently diagnosed cancer in men across developed countries (1) (2). According to the Surveillance, Epidemiology, and End results Program (SEER), the age-adjusted incident rate of prostate cancer was 137.9 per 100,000 men per year, based on 2008-2012 cases in the US. Based on this current trend, SEER estimated that nearly 14.0 percent of US men will be diagnosed with prostate cancer at some point during their lifetime. Also, prostate cancer ranks as the second most common cause of death in men above age 55 in the developed world (1). SEER reported the age adjusted mortality rate, based on 2008 to 2012 data, to be 21.4 per 100,000 men per year in the US. Prostate cancer is the second most common cause of death in Australia (2011) and Britain (2011), and the third most common in Canada (2008), New Zealand (2010) and European Union (2009) (1).

Prostate cancer incidence mortality rates were comparatively the lowest among Asian men in the past (3), but striking changes have occurred. The rates have increased in East Asia, especially the incidence rate, which more than doubled in Singapore and Japan compared to the period of 1980-1990. However, those rates remain lower than in most Western countries (23.1 per 100,000 in Korea in 2008 and 27.1 per 100,000 in Japan in 2006) (4) (5). Prostate cancer incidence rates of immigrants from Asia to western countries become higher compared to the rates in their home country. In a study among Chinese immigrant populations in Canada, prostate cancer incidence rates were found to be midway between those of Chinese still living in China and Canadians (6). The findings suggested that both race and environmental factors may play roles in prostate cancer rates.

In 2004, 62% of prostate cancer survivors were aged 70 years or older (7). Therefore, how to improve prostate cancer survivors' quality of life is another important topic, especially recently. One study found that both physical and psychological health problems can play important roles in prostate cancer survivors' quality of life. Unfortunately, further studies are still needed for an understanding of how to sustain benefits over the long term in prostate cancer survivors (8).

B. Analytical observational epidemiology

Since prostate cancer is an important public health issue, especially in the western world, a great deal of analytical observational epidemiology research has been done since the last century, trying to find prostate cancer risk factors. However, except for a few established risk factors, such as race, age, and family history, other factors are still in debate. Therefore, actual prostate cancer risk factors are poorly understood and further research is needed.

1.1 Age

Prostate cancer is less common among men under 50 years old with less than 0.1% among all diagnosed prostate cancer patients, and nearly 85% of cases of prostate cancer are diagnosed among men over 65 years old. It also has been found that the cumulative risk of developing prostate cancer at the age of 85 years ranges from 0.5% to 20% worldwide (9). Autopsy studies found microscopic prostate cancer lesions in 30% of men in their fourth decade, 50% of their sixth decade, and more than 75% of men after their eighth decade (10).

1.2 Race

African-American or Black men have a risk of diagnosis that is 1.6 times more than for whites, and the risk of death from prostate cancer is also 2.5 times

greater (11). Studies indicate that African-American men and Jamaican men of African descent have the highest incidence rates of prostate cancer in the world. In addition, men of Asian descent living in the United States have a lower prostate cancer risk compared to White or Black Americans. However, their risk of prostate cancer is higher than that of men of similar backgrounds who are still living in Asia (6, 11). Similar trends were found since the early 20th century and continued until now. Also, prostate cancer incidence rates differ widely among different ethnic groups, ranging from the lowest among Asian men (2.84 per 100,000 in certain area of China in 2008 (5)) to the highest among Americans (more than 80 per 100,000 in North America in 2008 (5)) (12).

1.3 Family history

As early as 1960, epidemiological studies found a familial aggregation of prostate cancers. Subsequent case-control and cohort studies supported this finding, finding that the relative risk for prostate cancer among those whose father or brother has prostate cancer was almost twice the risk among those who did not have a history of a first degree relative with prostate cancer (12). The risk of prostate cancer would be even higher for men who have several affected direct relatives, especially when their relatives are diagnosed with prostate cancer at a relatively young age (11). These data suggest that there may be an inherited genetic factor in some prostate cancer cases.

1.4 Diet and nutrition

Overall, epidemiologic studies conducted to date suggest that high intakes of saturated fat, meats cooked at high temperature, and calcium may be positively associated with prostate cancer risk, especially for advanced prostate cancer (13). However, inconsistent findings were also published, adding uncertainty on this topic (14). Fruit and vegetables may play a preventive role in prostate cancer, but further studies are in needed to make more solid conclusions (15). The effects of vitamins on prostate cancer risk were also reported differently among studies, leaving them as uncertain risk factors. However, it is hard to draw conclusions for a single dietary factor from dietary studies, partly because multicollinearity and interactions among dietary factors make those studies complicated and problematic when studying one factor without considering others (16).

1.5 Lifestyle

Different types of alcohol were found to have different associations with prostate cancer. For example, Schoonen *et al* in a frequency-matched case-control study (n = 1,456) in year 1993-1996 found that beer (adjusted OR=1.17, 95%CI 0.93-1.49) or liquor (adjusted OR=1.16, 95%CI 0.92-1.47) were not associated with prostate cancer risk, but red wine consumption was associated with a lower risk (adjusted OR=0.74, 95%CI 0.59-0.93) (17). Tea and coffee consumption may be inversely associated with prostate cancer, especially with advanced prostate cancer (18) (19). Cigarette smoking tends to be associated with higher risk of advanced prostate cancer (20). Physical activity has not been found to be associated with prostate cancer risk (21). However, since

inconsistent results were also found in other studies on lifestyle and prostate cancer, no solid conclusions can be drawn.

1.6 Infection and inflammation

Genitourinary infection, a highly suspected potential risk factor, has been extensively investigated in relation to prostate cancer risk for more than 30 years. A systematic review of published articles based on these 30 years of results shows that a meta-analysis based on literatures from 1966 to 2004 conducted by Taylor *et al*, which included 6,022 unique prostate cancer patients and 7,320 controls, found that a history of any STD was associated with a slightly increased prostate cancer risk (meta OR=1.6, 95% CI 1.26-1.73). However, a more recent large prospective study conducted by Huang *et al* did not observe an association between prostate cancer risk and a specific STD (22). Therefore, a possible role of genitourinary infection in prostate cancer etiology has yet to be determined.

1.7 Other important factors

Occupational exposures have long been considered potential risk factors for prostate cancer; however, there is still not enough evidence to implicate work-related ergonomic, physical, environmental, or psychosocial factors (23). However, some evidence implicates toxic metals, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons. Since farmers may have higher exposures to these and other factors, it is of interest to investigate farming as a high risk occupation for prostate cancer. Sexual and reproductive factors, such as sexual

activity, vasectomy, and circumcision, are also suspected as potential risk factors. However, associations of prostate cancer with these factors have been neither strong nor consistent. Endocrine factors were also investigated, but the results also have been inconsistent.

C. Clinical trials

There have also been some clinical trials for prostate cancer prevention. The largest and most well-known one is the Selenium and Vitamin E Cancer Prevention Trial (SELECT). SELECT, a randomized, double-blind, placebo-controlled, 2x2 factorial designed clinical trial, was conducted to evaluate the efficacy of selenium and vitamin E, alone and in combination, in reducing prostate cancer incidence (24). The initial study was stopped after 7 years because the accumulating data were indicating that neither selenium nor vitamin E supplements were appearing to be reducing the incidence of prostate cancer. Furthermore, there was a non-statistically significant increase in prostate cancer risk with vitamin E. An updated report in 2011 included 18 months of additional follow-up information on the initial study, showing that the vitamin E alone group had a 17% relative increase in prostate cancers compared to the placebo group, a finding that was statistically significant (25) .

D. Molecular basis of prostate cancer

The molecular pathogenesis of prostate cancer is becoming clearer. Generally, it is thought that germ-line mutations in the *RNASEL*, *ELAC2* or *MSR1* genes cause normal prostate epithelium to change to proliferative inflammatory atrophy (PIA). Then, if there are other factors that cause chromosome changes, such as chromosome 8q gain, chromosome 8p loss, or *GSTP1* CpG island hypermethylation, some areas of PIA

transition into prostatic intraepithelial neoplasia (PIN). With further mutation or chromosome changes in these areas of PIN, localized prostate cancer occurs. If there is *AR* gene mutation or amplification, localized prostate cancer will finally become metastatic (26).

E. Genetic epidemiology of prostate cancer

Genetic epidemiology studies have been interested in identifying genetic risk factors for prostate cancer for a long time, and many high-risk genes or alleles were found during these endeavors. The use of genome-wide association studies (GWAS) provides a more powerful tool for identifying such factors. Recently, via GWAS, more than 40 germline variants of various genes were found to be significantly associated with prostate cancer susceptibility among different ethnic groups (27). A meta-analysis on more than 10 million single-nucleotide polymorphisms (SNPs) among 43,303 prostate cancer cases and 43,737 controls including populations from almost all continents identified 23 novel susceptibility loci, which were revealed at $P < 5 \times 10^{-8}$ (28). In addition, this meta-analysis found that 33% of the familial risk of the disease in European populations could be explained by these 23 prostate cancer risk variants when combined with the previously known variants. Another recent meta-analysis was conducted of 20 genetic variants in 19 different genes among 584,100 subjects (29). The results showed that the average meta-OR was 1.33 for risk alleles (95% CI 1.02 - 3.79), and it was 0.84 for protective alleles (95% CI 0.76 - 0.90).

F. Screening for prostate cancer

PSA-based screening used to be a very popular way to test and diagnose early stage prostate cancer. However, PSA-based screening for prostate cancer was found to lead to substantial over-diagnosis and over-treatment. The over-diagnosis rate of prostate cancer is of important concern since a man cannot benefit from screening or treatment if the cancer would remain asymptomatic for the remainder of his life (30). Therefore, universal PSA-based screening for prostate cancer is no longer the recommended primary screening method. The current practice in most developed countries is that patients can still request PSA testing, but positive results should be combined with other evidence, such as transrectal ultrasound or prostate biopsy (31).

G. Farming and prostate cancer

Studies suggest that, because of the use of pesticides, farming may be an occupational risk factor for prostate cancer (32). Besides pesticides exposure, which is the primary hypothesized risk factor, there are several other hypotheses about possible risk factors for prostate cancer among farmers. Even though multiple studies on farming and prostate cancer have been conducted, trying to clarify this association, the findings have been inconsistent (33). Based on a literature review of articles published after 1990, a total of 9 epidemiologic publications about farming and prostate cancer were found. Among them, one was a meta-analysis, three focused on pesticide use, two discussed cadmium, and three were of general risk factors for prostate cancer among farmers. The meta-analysis focused on 37 studies to assess whether farmers had higher risk for several cancers, including prostate cancer. It concluded that there was a slightly higher prostate cancer risk among farmers (meta-RR=1.07, 95%CI 1.02-1.13), but that this differed by geographic location and study design (32). Band *et al.* found that their results

for some pesticides, including DDT, simazine and lindane, were consistent with existing findings. However, their results for some other pesticides were different from those previously reported, for example, for captan, diazinon, and dicamba (34). Findings from Cockburn *et al.* supported the association of pesticides exposure with prostate cancer risk (35). A meta-analysis regarding pesticides found that, although prostate cancer cases were almost four times more likely to be farmers, the reported pesticides exposure was inversely associated with prostate cancer (OR=0.68, 95% CI 0.49-0.96) (33). Therefore, the author pointed out that the higher prostate cancer risk among farmers may not due to exposure to pesticides. These three papers about pesticides did not agree with each other, and also did not totally agree with previous findings as they mentioned in their articles. The studies on cadmium also had discrepancies with each other. Goyer *et al.* mentioned that an epidemiological association concerning occupational cadmium exposure and prostate cancer is still unclear despite suggestive results in rats (36). Sahmoun *et al.* concluded that epidemiological studies do not convincingly implicate cadmium as a cause of prostate cancer (37). The remaining articles discussed general prostate cancer risk factors among farmers, which will be elaborated in the following sections.

1. Pesticides exposure

Pesticides have long been considered to be potential occupational risk factors for prostate cancer among farmers. Proposed mechanisms include that a variety of pesticides can affect hormone functioning by mimicking hormones or affecting enzyme systems involved in hormone metabolism. Variations in hormone levels may affect prostate cancer risk since normal growth of the prostate gland is dependent on a critical balance of levels of sex hormones, such as androgens (35). Certain

pesticides that affect androgenic stimulation of the prostate may potentially lead to increased cell proliferation and cancer. However, research findings have not always supported this theory. A recent meta-analysis conducted by Ragin included ten published and two unpublished studies, with a total of 3,978 cases and 7,393 controls (33). They found that prostate cancer cases were almost four times more likely to be farmers compared with controls with benign prostate hyperplasia (BPH; meta odds ratio (OR)=3.89, 95% confidence interval (CI)=1.96-7.48), but 1.38 times more likely when compared with non-BPH controls (meta OR=1.38, 95% CI=1.16-1.64). However, reported pesticides exposure was found to be inversely associated with prostate cancer (meta OR=0.68, 95% CI=0.49-0.96), and no association with exposure to fertilizers was observed. Thus, their findings suggested that farming is a risk factor for prostate cancer, but that exposure to pesticides may not be the primary reason for the higher risk.

2. Cadmium exposure

Cadmium (Cd), as well as its compounds, were established as human and animal carcinogens, and classified as “Carcinogenic to Humans (Group 1)” by IARC in 1993 (38) (39). Nevertheless, epidemiological support for occupational cadmium exposure in relation to prostate cancer is still unclear despite suggestive results in from rat studies (36). A review by Sahmoun *et al.*, which included articles for cadmium and prostate cancer in the MEDLINE database from 1966 to 2002, concluded that epidemiological studies do not convincingly implicate cadmium as a cause of prostate cancer, which is in contrast to laboratory studies (37). No further confirmative studies or findings are available since then. Therefore, further

epidemiological studies are still needed to clarify whether there may be a relationship between cadmium exposure and prostate cancer.

3. Other exposures

There are also other hypotheses about farming and prostate cancer. Gulden and Vogelzng suggested that there are several possible harmful occupational exposures that might increase risk for prostate cancer among farmers (40). The first suggestion is grain dust. However, grain dust itself is unlikely to be carcinogenic; instead, dusts that contain fungal components may be noxious. Livestock was also suggested, since exposure to animal viruses, bacteria, and fungi exposures plausibly could be considered as potential risk factors. They also suggested that diesel exhaust fumes from tractors and other agricultural machinery may be related to prostate cancer risk; however, no association was found by most studies that investigated the association of exposure to exhaust fumes with prostate cancer. However, overall, the likelihood that these three suggestions of occupational exposures are the main risk factors for prostate cancer among farmers is very limited and needs further research.

4. Harmful lifestyle

The incidence rates for most types of cancers are generally low in agricultural workers, in part due to the low prevalence of cigarette smoking and alcohol consumption, and higher levels of physical activity from farm work among this group (41). Nevertheless, farmers are likely to consume more dairy products, for instance, milk, meat, and eggs, compared to men in average households, especially if they produce dairy products on their farm (40). As discussed in the previous analytical

observational epidemiology section above, dairy intake may be a risk factor for prostate cancer (13). Therefore, the high proportion of fat consumption in their daily diet may have a positive impact on their higher prostate cancer risk.

5. Other possible risk factors

There are also many other potential risk factors, but they may play a minor role or there have been no reported studies that investigated them. For example, differences in the detection rate for prostate cancer among farmers could be caused by differences in medical screening (40). Also, it is possible that since fathers tend to pass on the farm and the passion for farming to their sons, the higher risk of prostate cancer may result from a positive family history of the disease. However, epidemiological studies are needed to support these potential hypotheses.

H. Introduction of study purpose

Age, race, and family history are established risk factors for prostate cancer (9). Other possible prostate cancer risk factors, although in debate, mainly include diet/nutrition, lifestyle, infection/inflammation, and endocrine factors (10-20). Pesticides or cadmium exposure, as well as other exposures or some other particular reasons discussed above, are commonly considered as risk factors for prostate cancer among farmers. However, most of these other prostate cancer risk factors are not widely accepted. More and Larger studies are still needed to investigate the true risk factors. This study would serve as a pilot study for a larger and more complicated study in the future.

For this pilot research, the main purpose is to investigate whether being a farmer is associated with risk for prostate cancer, controlling for other possible risk factors. A second aim

is to investigate whether a farming-prostate cancer association differs by localized versus advanced prostate cancer. A third aim is to investigate whether the farming-prostate cancer association differs according to other risk factors for prostate cancer.

Abstract

Prostate cancer is the most frequently diagnosed major cancer in men across the world. It has been hypothesized that farmers may be of higher risk for prostate cancer because of their various occupation-related exposures; however, epidemiologic findings regarding this have been inconsistent. To investigate an association of farming with prostate cancer risk, we analyzed data from a previously conducted, community-based case-control study with 113 newly diagnosed incident prostate cancer cases and 258 age and race frequency-matched controls in the Piedmont Triad area of North Carolina from 1994 to 1996. All participants were interviewed, completed questionnaires, and provided blood and urine samples at a study visit. Visits for cases were within two weeks of diagnosis and prior to initiation of any treatment. The estimated adjusted odds ratio (OR) for the farmer-prostate cancer association was 1.63 (95% confidence interval [CI] 0.97 - 2.73), for advanced prostate cancer it was 4.77 (95% CI 1.56 - 14.58), and for those less than 67 years of age it was 2.69 (95% CI 1.24 - 5.84). The findings from this pilot study suggest that farmers may be at higher risk for prostate cancer, perhaps especially for more advanced or aggressive disease.

Key words

Prostate cancer; farming; case-control study

Background

Prostate cancer is the most common non-skin malignancy affecting men in the United States and across developed countries (1) (2). There have been numerous analytical observational epidemiology studies on prostate cancer. However, except for a few established risk factors, such as race, age, and family history of prostate cancer, other risk factors are still unclear.

It has been hypothesized that farmers may be at higher risk for prostate cancer because of their various occupational exposures, including, but not limited to, pesticides, which may have mutagenic and sex hormone-related effects (32). Other farming exposures of interest have included cadmium, grain dusts, fungi, livestock-related infectious agents, and aromatic hydrocarbons. It is also possible that higher risk in farmers may result from multiple exposures that collectively increase risk. Even though multiple studies on farming and prostate cancer have been conducted, trying to clarify this association, the findings have been inconsistent (33). From a meta-analysis of 37 articles published after 1990, a slightly higher risk for prostate cancer among farmers was found (meta-RR=1.07, 95%CI 1.02-1.13), (32). In a more recent meta-analysis of 10 published and two unpublished studies, with a total of 3,978 cases and 7,393 controls (33), it was found that that prostate cancer cases were almost four times more likely to be farmers relative to controls with benign prostate hyperplasia (BPH; meta odds ratio (OR)=3.89, 95% confidence interval (CI)=1.96-7.48), but 1.38 times more likely relative to non-BPH controls (meta OR=1.38, 95% CI=1.16-1.64). However, reported pesticides exposure was inversely associated with prostate cancer (meta OR=0.68, 95% CI=0.49-0.96), and no association with exposure to fertilizers was observed. The results of studies on cadmium, which was classified as "Carcinogenic to Humans (Group 1)" by IARC in 1993 (38) (39), have been discrepant (36) (37), possibly because the published studies were limited by not having

biomarkers of cadmium exposure. Investigation of other possible risk factors that may be of particular relevance to farmers has been limited. Among the farming-prostate cancer studies, none reported the association according to tumor stage or age.

To address the plausible but still unclear farming-prostate cancer association, we conducted a pilot case-control study. The main purpose was to investigate whether being a farmer is associated with prostate cancer, controlling for other possible risk factors. A second aim was to investigate whether a farming-prostate cancer association differs by localized versus advanced prostate cancer. A third aim was to investigate whether the farming-prostate cancer association differs according to other risk factors for prostate cancer, including cadmium exposure as assessed by a biomarker of cadmium exposure.

Methods

Subject recruitment

This community-based case-control study of prostate cancer was conducted in the Piedmont Triad area of North Carolina from 1994 to 1996. It was approved by the Committee for Human Research at Wake Forest University, Winston-Salem, North Carolina, and all participants provided informed consent. A total of 113 prostate cancer cases and 258 controls were recruited from the same geographic region. All cases and controls were men, black or white races, over 50 years old and English speaking. Cases were newly diagnosed with prostate cancer during the study period in area urology and radiation oncology practices, and attended the study visit before surgery or radiation treatment began. Controls were selected by a random procedure using the Polk Directory and a commercial telemarketing household-based list, from the same source population as the cases. Controls were not screened for prostate cancer as part of the study because funding for it was prohibited in NIH-funded studies at the time; however, data on PSA testing were collected. Study participants had no history of prostate disease, prostate surgery, active tuberculosis, current liver/kidney disease, or any kind of cancer except for non-melanoma skin cancer.

Data collection

All participants, including cases and controls, attended a four- to five-hour study visit in the General Clinical Research Center at Wake Forest University. Informed consent procedures; interviews; completing a block food frequency questionnaire, medical history and lifestyle questionnaires; and providing blood and urine samples were conducted at the same visit. Participants were asked about socio-economic variables, occupational exposures, exercise

frequency, smoking, drinking, sex partners, venereal diseases, and family history of prostate cancer and breast cancer in the medical and lifestyle questionnaires. The food frequency questionnaire queried about usual intakes over the past 12 months and contained 18 questions on general nutrition and food use and questions on the frequency and quantity of 99 food items in 8 categories, including 12 fruits, 22 vegetables, 18 meats, 9 breads, 10 breakfast foods, 7 sweets, 5 dairy products, and 16 beverages. Urinary cadmium was measured in triplicate using the atomic absorption method, and its concentration was normalized to the urinary creatinine concentration.

Detailed prostate cancer information on cases was obtained from the North Carolina Cancer Registry, and included TNM and SEER cancer stage, but not Gleason's score. For stratified analyses, prostate cancer cases were dichotomized as localized versus advanced prostate cancer cases based on their SEER stage. Localized prostate cancer included in situ and localized stages, whereas advanced prostate cancer included regional and distant stages.

Data analysis

Descriptive characteristics of cases and controls were calculated and compared using the two-sample t-test for continuous variables, and the chi-square test for categorical variables. Descriptive comparisons of farmers and non-farmers were also calculated in a similar manner.

An association of farming with prostate cancer was estimated using multivariable unconditional logistic regression, with non-farmers as the referent group. Prostate cancer was first analyzed as a dichotomous outcome, and then, using polytomous multivariable logistic regression, as a three-level outcome with prostate cancer categorized as localized or advanced prostate based on SEER stage. Our primary exposure variable, farming, was first analyzed as all

farmers combined, and then we categorized farmers according to whether they reported occupational exposure to pesticides. After examining the crude associations, multivariable adjusted models were built. Potential covariates were chosen based on biological plausibility and previous literature, and included age, race, family history of prostate cancer in a first degree relative, physical activity, body mass index (BMI), smoking, alcohol use, total energy and fat intakes, dietary calcium intake as an indicator of daily dairy food intakes, total (dietary + supplemental) calcium intake, history of circumcision or vasectomy, history of a sexually transmitted infection (STD), and urinary cadmium/creatinine ratio. Criteria for inclusion in the models included biological plausibility, associations of the covariates with farming and prostate cancer in our study, consideration of directed acyclic graphs, and the impact of inclusion/exclusion of the covariate had on the estimated farming-prostate cancer association. Final covariates in the model included age, race, and family history of a first degree relative with prostate cancer, current alcohol use, urinary cadmium/creatinine ratio, and a history of a STD. Because cadmium, dietary calcium (as an indicator of dairy food intakes), total calcium, and pesticide use could be considered as both confounders and intermediates for the farming-prostate cancer association, for sensitivity analyses, we examined models with and without these variables.

Multivariable-adjusted associations of a history of being a farmer with incident prostate cancers were also estimated according to selected prostate cancer risk factors. Where indicated, multiplicative interaction terms were tested in the models. Based on literature review, seven potential interaction variables with farming were identified: age, race, family history of prostate cancer in a first degree relative, STD history, urinary cadmium/creatinine, dietary calcium intake (as an indicator of dairy food intakes), and total calcium consumption.

Age, dietary and total calcium intakes, and urinary cadmium/creatinine were dichotomized based on the median values in the controls.

All analyses were conducted using SAS (Statistical Analysis System) software, version 9.3, developed by SAS institute (Cary, NC). The statistical significant level was selected as 0.05 for all analyses.

Results

Selected characteristics of the cases and controls are summarized in Table 1. Cases and controls on average were of similar age and had comparable race distributions. However, compared to controls, cases had greater proportions of a history of being a farmer (34% vs. 24.7%) and of having a first degree relative with diagnosed prostate cancer (13.3% vs. 9.3%). Also, cases were modestly more likely to smoke, less likely to drink alcohol, and more likely to report a history of a STD. Other characteristics, including mean total fat and energy intakes, mean dietary and total calcium intakes, history of circumcision, and mean urinary cadmium and creatinine ratios, were similar between cases and controls. A total of 62% of the controls reported ever having had a PSA test.

Selected characteristics of the study participants according to a history of being a farmer are summarized in Table 2. Among the 371 participants, 15 (4%) did not answer the question about ever being a farmer or not, and another two (0.5%) did not report their race, leaving 354 participants for this analysis. Farmers were substantially more likely to have been exposed to pesticides (28.9% vs. 5.3%), less likely to drink, be circumcised, or report a history of a STD, and, on average, consumed more fat.

The crude and multivariable-adjusted associations of ever being a farmer, overall and categorized according to occupational pesticide use, with prostate cancer overall and by stage are shown in Table 3. Among all farmers, there was a multivariable-adjusted estimated 1) 63% higher risk for prostate cancer overall, a finding that was nearly statistically significant; and 2) a statistically significant nearly 5-fold higher risk for advanced prostate, but only an estimated 40% higher risk for localized prostate cancer, a finding that was not statistically significant. As noted in Table 3, the sample size for assessing the farming-prostate cancer association according

to pesticide use was small. However, the estimated risks for all prostate cancers combined were similar for farmers who did or did not use pesticides (92% and 56% higher, respectively, and neither estimate was statistically significant). Inclusion or exclusion of urinary cadmium/creatinine, dietary calcium, total calcium, and pesticide use did not produce substantial changes in the estimated farming-prostate cancer association (data not shown).

The results of the stratified analyses are shown in Table 4. The farmer-prostate cancer association was higher among those less than the median age of 67 years, and tended to be higher among those without a family history of prostate cancer in a first degree relative, those with higher cadmium exposures, those who reported no history of a STD, those who had higher total calcium intakes, and those who had lower dietary calcium intakes. However, the only statistically significant estimated association was among those less than 67 years of age (OR 2.69; 95% CI 1.24-5.84).

Discussion

The results of this study suggest that farmers may be at higher risk for prostate cancer, especially advanced prostate cancer and at a younger age. The latter findings suggest that farmers may be at particularly higher risk for more aggressive disease. To our knowledge, this is the first study of farmers and prostate cancer risk to report findings by prostate cancer stage and age.

There are several hypotheses regarding the plausibility of a farming-prostate cancer association. One of the most prominent is occupational pesticide exposure. It is known that variations in hormone levels may affect prostate cancer risk since normal growth of the prostate gland is dependent on a critical balance of levels of sex hormones, such as androgens (35). A variety of pesticides have the potential to increase prostate cancer risk since they can affect hormone functioning by mimicking hormones or affecting enzyme systems involved in hormone metabolism. Certain pesticides that affect androgenic stimulation of the prostate may increase cell proliferation and eventually lead to cancer occurrence. Another common hypothesis is related to occupational cadmium (Cd) exposure. The reason is that cadmium, as well as its compounds, were established as human and animal carcinogens, and classified as “Carcinogenic to Humans (Group 1)” by IARC in 1993 (38) (39). Other hypotheses include grain dusts with noxious fungal contaminants; exposure to animal viruses, bacteria, and fungi; and diesel exhaust fumes from tractors and other agricultural machinery; however, evidence for or against these hypotheses is limited.

In the published literature on prostate cancer in farmers, inconsistent results were reported. A meta-analysis in 1998 of 37 studies to assess whether farmers are at higher risk for cancer, found a slightly higher risk for prostate cancer (meta-RR=1.07, 95% CI 1.02-1.13), a finding that

differed by geographic location and study design (32). A more recent meta-analysis reported by Ragin in 2013, included 10 published and two unpublished studies, with a total of 3,978 cases and 7,393 controls (33). They found that prostate cancer cases were almost four times more likely to be farmers relative to controls with benign prostate hyperplasia (BPH; meta odds ratio (OR)=3.89, 95% confidence interval (CI)=1.96-7.48), but 1.38 times more likely relative to non-BPH controls (meta OR=1.38, 95% CI=1.16-1.64). However, reported pesticides exposure was found to be inversely associated with prostate cancer (meta OR=0.68, 95% CI=0.49-0.96), and no association with exposure to fertilizers was observed. In our study, the farming-prostate cancer association was slightly stronger among farmers who used pesticides; however, the risk estimates in the strata were not statistically significant and the confidence intervals for the estimates in the strata overlapped. Therefore, a possible role of pesticides exposure in the farming-prostate cancer association remains unclear.

As noted above, it has been proposed that cadmium exposure may be another factor involved in a farming-prostate cancer association. A meta-analysis that included 25 papers in the Medline database from 1966-2002 focused on the association of occupational cadmium exposure and prostate cancer risk. The findings included that among four descriptive studies, three (75%) reported positive associations; among 10 case-control studies, five (50%) reported positive associations; and among 11 cohort studies, three (27%) reported positive associations (35). In our study, the farming-prostate cancer association differed minimally upon exclusion/exclusion of the urinary cadmium/creatinine ratio, and it was somewhat stronger among those with a higher urinary cadmium/creatinine ratio; however, the risk estimates were not statistically significant and the confidence intervals for the estimates in the strata overlapped. Thus, a possible role of cadmium exposure in the farming-prostate cancer association also remains unclear.

None of the studies included in the three meta-analyses discussed above investigated localized and advanced prostate cancers separately. Therefore, our results suggest that the inconsistencies among studies on farming and prostate cancer could be attributable to differences in the proportions of localized and advanced prostate cancer cases among those studies. In other words, we hypothesize that, if there is a high proportion of advanced prostate cancer cases in the study population, the association of farming with prostate cancer would more likely be stronger and statistically significant. In addition, none of these studies reported associations stratified on age. Our study is the first to report such an analysis, finding that the farming-prostate cancer association was significantly higher among those less than the median age of 67 years (OR 2.69 vs. 0.99).

Strengths of this study include the in-person data collection procedures, the community-based design, and studying prostate cancer cases within days of diagnosis and before initiation of any treatments, which, respectively, were to enhance the accuracy and completeness of data collection, improve representativeness, and reduce recall bias. Another strength was the inclusion of a biomarker of cadmium exposure. However, like most case-control studies, this study also has inherent limitations, including possible recall bias and temporal ambiguity. A total of 38% of the controls had no history of being screened for prostate cancer, and some of them may have been undiagnosed cases, which may have attenuated our results. A major limitation of this study was the small sample size, especially for stratified analyses. Although our finding of a stronger association for advanced prostate cancer was statistically significant, the point estimate was relatively imprecise, given that there were only 18 participants with advanced prostate cancer. Also, our assessment of pesticide exposure was limited, our number of farmers who had occupational exposure to pesticides was quite small, and we did not assess other farming-related exposures, such as diesel exhaust fumes, grain dust, or livestock exposures. This

meant that we were unable to meaningfully address the question of whether the farming-prostate cancer association was related to pesticide use vs. other farming-related exposures. A history of a STD was self-reported, and with the small proportion of participants who reported such a history, it was not possible to assess confounding by STD type. However, the results of this pilot study support further investigation of farming and prostate cancer risk.

In summary, the results from this pilot case-control study, taken together with previous literature, support further investigation of whether farmers may be at higher risk for prostate cancer, especially more aggressive disease, and if so, why they may be at higher risk. Larger, more focused and preferably prospective studies are needed.

Table 1. Characteristics of men diagnosed with incident prostate cancer and controls, Piedmont Triad Area, North Carolina, U.S., 1994-1996 (N = 371)

	Cases (N = 113)	Controls (N = 258)	P-value ^a
Age (years) ^b	66.1 (7.5)	67.0 (7.6)	0.87
Race (%)			
Black	15.2	14.4	
White	84.8	85.6	0.85
1° relative with prostate cancer (%)	13.3	9.3	0.26
Farmer ever (%)	33.9	24.7	0.07
Former pesticides user (%)	26.4	20.0	0.34
Physical activity (%)			
Light	21.2	23.4	
Moderate	69.0	69.3	
Vigorous	9.73	7.39	0.71
BMI ^c (kg/m ²)	26.9 (3.6)	27.3 (3.8)	0.38
Currently smoke (%)	13.3	9.4	0.26
Currently drink (%)	47.1	54.7	0.24
Total fat consumption (g/day)	83.7 (40.8)	82.0 (41.2)	0.72
Total energy intake (kcal/day)	1,939 (809)	1,901 (798)	0.68
Dietary calcium intake (mg/day)	753 (353)	774 (373)	0.63
Total ^d calcium intake (mg/day)	801 (373)	822 (409)	0.48
Circumcised (%)	43.8	45.2	0.79
Vasectomy (%)	23.6	26.6	0.55
History of STD ^e (%)	14.3	9.8	0.22
Urinary cadmium/creatinine ^f ($\mu\text{g}/\text{mg} \cdot 10^4$)	6.7 (7.3)	6.6 (6.0)	0.86

^a Two sided p-values from two-sample t-test for continuous variables, and chi-square test for categorical variables

^b Mean (standard deviation) presented for continuous variables and percent presented for categorical variables, unless otherwise indicated

^c BMI, body mass index

^d Total = dietary + supplemental

^e STD, sexually transmitted disease

^f Ratio of cadmium (measured via atomic absorption) to creatinine in a spot urine sample

Table 2. Characteristics of farmers and non-farmers, Piedmont Triad Area, North Carolina, U.S., 1994-1996 (N = 371).

	Farmers (N = 98)	Non-farmers (N = 258)	P-value ^a
Age (years) ^b	67.7 (7.3)	66.4 (7.6)	0.16
Race (%)			
Black	11.2	15.6	0.29
White	88.8	84.4	
1° relative with prostate cancer (%)	8.2	11.7	0.34
Pesticides exposure (%)	28.9	5.3	0.003
Physical activity (%)			
Light	20.6	24.0	0.77
Moderate	70.1	67.8	
Vigorous	9.3	8.1	
BMI ^c (kg/m ²)	27.3(3.9)	27.1 (3.7)	0.77
Currently smoke (%)	9.4	11.2	0.61
Currently drink (%)	32.9	60.4	<0.001
Total fat consumption (g/day)	88.3 (39.4)	79.9 (41.2)	0.09
Total energy intake (kcal/day)	1,978 (682)	1,873 (828)	0.23
Dietary calcium intake (mg/day)	793 (340)	758 (372)	0.43
Total ^d calcium intake (mg/day)	839 (368)	806 (404)	0.49
Circumcised (%)	33.7	48.4	0.01
Vasectomy (%)	23.7	26.4	0.61
History of STD ^e (%)	7.0	12.9	0.14
Urinary cadmium/creatinine ^f ($\mu\text{g}/\text{mg} \cdot 10^4$)	7.5 (6.8)	6.4 (6.3)	0.19

^a Two sided p-values from two-sample t-test for continuous variables, and chi-square test for categorical variables

^b Mean (standard deviation) presented for continuous variables and percent presented for categorical variables, unless otherwise indicated

^c BMI, body mass index

^d Total = dietary + supplemental

^e STD, sexually transmitted disease

^f Ratio of cadmium (measured via atomic absorption) to creatinine in a spot urine sample.

Table 3. Associations of a history of being a farmer with risk for prostate cancer in the Piedmont Triad Area, North Carolina, U.S., 1994-1996 (N = 371).

	Cases	Controls		Cases	Crude Associations		Adjusted Associations ^a	
					OR	95% CI	OR	95% CI
All prostate cancer	113	258	Non-farmers	72	1.00	--	1.00	--
			Farmers	37	1.57	0.96 - 2.56	1.63	0.97 - 2.73
Localized prostate cancer ^b	82	258	Non-farmers	54	1.00	--	1.00	--
			Farmers	25	1.41	0.81 - 2.46	1.40	0.78 - 2.52
Advanced prostate cancer ^c	18	258	Non-farmers	9	1.00	--	1.00	--
			Farmers	9	3.05	1.16 - 8.03	4.77	1.56 - 14.58
All prostate cancer	113	258	Non-farmers and non-pesticides users	72	1.00	--	1.00	--
			Farmers but non-pesticides users	25	1.47	0.84 - 2.57	1.56	0.86 - 2.81
			Farmers and pesticides users	12	1.94	0.87 - 4.30	1.92	0.85 - 4.33
Localized prostate cancer	82	258	Non-farmers and non-pesticides users	54	1.00	--	1.00	--
			Farmers but non-pesticides users	18	1.41	0.75 - 2.64	1.42	0.74 - 2.76
			Farmers and pesticides users	7	1.51	0.59 - 3.85	1.45	0.56 - 3.77
Advanced prostate cancer	18	258	Non-farmers and non-pesticides users	9	1.00	--	1.00	--
			Farmers but non-pesticides users	6	2.82	0.95 - 8.33	5.02	1.45 - 17.4
			Farmers and pesticides users	3	3.88	0.95 - 15.8	4.52	0.92 - 22.2

^a Adjusted for age, race, history of prostate cancer in a first degree relative, current alcohol use, urinary cadmium/creatinine, and sexually transmitted disease history

^b Localized prostate cancer defined as SEER in situ or localized stages

^c Advanced prostate cancer defined as SEER regional or distant stages

Table 4. Multivariable adjusted associations ^a of a history of being farmers with incident prostate cancers according to selected prostate cancer risk factors, Piedmont Triad Area, North Carolina, U.S., 1994-1996 (N = 371).

		N ^b	OR	95% CI
Family history of prostate cancer ^b	Yes	39	0.74	0.12 - 4.76
	No	331	1.71	0.99 - 2.95
Race	White	315	1.44	0.82 - 2.52
	Black	54	1.80	0.39 - 8.29
Age	< 67 yrs.	176	2.69	1.24 - 5.84
	≥ 67 yrs.	195	0.99	0.48 - 2.05
Cadmium/ Creatinine ^c	< 5.34 µg/mg*10 ⁴	196	1.47	0.72 - 3.00
	≥ 5.34 µg/mg*10 ⁴	175	2.11	0.97 - 4.62
STD history	Yes / Unknown ^d	68	1.12	0.33 - 3.78
	No	303	1.69	0.96 - 2.98
Daily dietary calcium intake	< 690 mg	189	1.84	0.85 - 4.01
	≥ 690 mg	182	1.42	0.65 - 3.10
Total ^e daily calcium intake	< 758 mg	210	1.39	0.67 - 2.89
	≥ 758 mg	161	1.92	0.83 - 4.42

^a Adjusted for age, race, history of prostate cancer in a first degree relative, current alcohol use, urinary cadmium/creatinine, and sexually transmitted disease history

^b In a first degree relative

^c Ratio of cadmium (measured via atomic absorption) to creatinine in a spot urine sample, dichotomized based on median of distribution in controls

^d Participants who skipped the question

^e Total = dietary + supplemental

Chapter III – Public Health Implications and possible future directions

Our study, to our knowledge, is the first to assess a farmer-prostate cancer association according to localized and advanced disease, age, and a biomarker of cadmium exposure. Prostate cancer is the most common non-skin malignancy affecting men in the United States (1). Many epidemiologic studies have been conducted to identify risk factors for prostate cancer, but only a few of the studies were focused on farming and prostate cancer. Among those few prostate cancer studies that investigated farmers, almost all only studied all prostate cancer cases combined. Our findings suggest that if farming increases risk for prostate cancers, it may be particularly for advanced prostate cancer and younger onset disease, both suggesting that farming may increase risk for more aggressive disease.

Based on the findings from this preliminary study and considering the findings of previously reported studies, the next logical step would be to conduct a large prospective cohort study with a large number of farmers, and more accurate assessment of multiple risk factors that may be related to farming, such as pesticide exposure. Such a study should also include, as we did, measurement of a urinary cadmium to creatinine ratio. A cohort study may provide a more unbiased result than a case-control study since it would not be susceptible to recall bias. A larger study population is also needed to get a more accurate point estimate with a higher degree of confidence. Researchers need to pay special attention to pesticide exposure measurements, since both dosage and type of pesticides could explain the association of farming with prostate cancer risk. Pesticide usage needs to be measured as accurately as possible. Special exposure also needs to be paid to farming-related exposures other than pesticides and cadmium. Also, various potential confounders mentioned in the literature and measured in the pilot case-

control study would need to be assessed properly. Careful attention should be paid to assessing SEER stage and Gleason's score.

If our hypothesis is eventually proven true, the knowledge could be used for public health prevention, including farmers' education, enhanced screening among farmers, and targeted safeguards to reduce certain exposures.

In conclusion, our study, to our knowledge, is the first to assess a farmer-prostate cancer association according to localized and advanced disease and age. However, because of the small sample size and the inherent disadvantages of case-control studies, a large prospective cohort study is needed to further investigate our findings. If our findings are eventually conclusively supported, they would be of great public health importance.

Appendix

Table 1. Odds Ratios for farmer status and prostate cancer, adjusting for each covariate one at a time for forward model selection.

Adjusted covariates	Odds Ratio (OR) among farmers and non-farmers	95% Confidence Interval (CI)	P-value for OR
None	1.57	0.96 - 2.56	0.07
Age, Race, and 1° family history			
Without additional covariate	1.66	1.01 - 2.73	0.05
With Physical activity	1.68	1.04 - 2.81	0.04
With Current smoking	1.71	1.05 - 2.87	0.03
With Current drinking	2.14	1.18 - 3.87	0.01
With Total daily fat consumption	1.59	0.96 - 2.64	0.07
With Total daily energy intake	1.60	0.96 - 2.64	0.07
With daily dietary calcium intake	1.61	0.98 - 2.67	0.06
With daily total calcium intake	1.62	0.98 - 2.68	0.06
With circumcised	1.69	1.02 - 2.81	0.04
With Vasectomy	1.72	1.03 - 2.85	0.04
With History of STD	1.70	1.00 - 2.89	0.05
With Urinary cadmium/creatinine	1.79	1.07 - 3.00	0.03

Table 2. Odds Ratios for farmer status and prostate cancer, adjusting for covariates selected from forward model selection process and adding remaining covariates one at a time.

Adjusted covariates	Odds Ratio (OR) among farmers and non-farmers	95% Confidence Interval (CI)	P-value for OR
Age, Race, 1°FH, Current Drinking and Urinary cadmium/creatinine	1.58	0.95 - 2.63	0.08
Add physical activity	1.67	0.96 - 2.68	0.07
Add current smoking	1.63	0.98 - 2.72	0.06
Add total daily fat consumption	1.52	0.91 - 2.55	0.11
Add total daily energy intake	1.52	0.91 - 2.55	0.11
Add daily dietary calcium intake	1.54	0.92 - 2.58	0.10
Add total daily calcium intake	1.65	0.97 - 2.81	0.07
Add circumcised	1.63	0.97 - 2.73	0.07
Add Vasectomy	1.63	0.97 - 2.73	0.07
Add History of STD	1.73	0.99 - 3.03	0.05
Subtract urinary Cd/creatinine	1.67	0.99 - 2.84	0.06
Add Pesticide use	1.57	0.95 - 2.62	0.08

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