EXHIBIT 116

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	Case No. 16-md-02741-VC MDL No. 2741
This document relates to: ALL ACTIONS	

EXPERT REPORT OF JENNIFER R. RIDER, ScD.

7/31/2017

TABLE OF CONTENTS

EXPERT REPORT OF JENNIFER R. RIDER, SCD, MPH

I. CREDENTIALS AND QUALIFICATIONS

As detailed in my curriculum vitae, attached as Exhibit A, I received a Bachelor of Science degree from the University of Wisconsin-Madison, a Master of Public Health degree from the University of Massachusetts-Amherst, and a Doctorate of Science degree in Epidemiology from the Harvard T.H. Chan School of Public Health (formerly Harvard School of Public Health).

In 2009, I received an academic appointment at Harvard Medical School and in 2011 I was appointed Assistant Professor at the Harvard T.H. Chan School of Public Health. I am currently Assistant Professor of Epidemiology, Boston University School of Public Health; Adjunct Assistant Professor, Harvard T.H. Chan School of Public Health; a Faculty Member of the Dana Farber Harvard Cancer Center; and a Faculty Member of the Boston University/ Boston Medical Center Cancer Center.

My teaching is primarily based at the Boston University School of Public Health, where I direct a course on intermediate epidemiology methods. I also frequently lecture in courses on cancer epidemiology and cancer prevention at both Boston University and the Harvard T.H. Chan School of Public Health. In addition, I teach a course on cancer screening at the National Cancer Institute Summer Curriculum in Cancer Prevention. In 2016, I began directing an intensive one-week summer course on cancer epidemiology and cancer prevention at the National Institute of Public Health (Instituto Nacional de Salud Publica) in Mexico. I advise several MPH and doctoral students at Boston University and Harvard.

My editorial board responsibilities include Statistical Reviewer, *Menopause* (2009-2014); and Associate Editor, *Cancer Causes and Control* (2015-present). I have conducted peer reviews for more than 20 journals, including the *British Medical Journal, European Urology, Cancer Research,* and *Clinical Cancer Research.*

I have authored, or co-authored, over 70 articles in the medical literature. Most of these articles pertain to case-control or cohort studies. I have published articles in a variety of well-respected medical journals including two articles in the *New England Journal of Medicine*; five articles in *European Urology*, the highest impact urological

journal; three in the *Journal of Clinical Oncology*; five in the *Journal of the National Cancer Institute*; and 3 in *Cancer Research.*

I have received the following honors and awards: Certificate of Distinction in Teaching – Office of the Dean for Undergraduate Education, Harvard College (2007); Teaching Commendation – Committee for Educational Policy, Harvard T.H. Chan School of Public Health (2011-2013); First Place Abstract – Prostate Cancer Foundation (2012); Best Poster in Session – American Urological Association (2012); Michael and Lori Milken Prostate Cancer Foundation Young Investigator Award – Prostate Cancer Foundation (2012); The Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine – Harvard Medical School (2013); and Best Clinical Research Paper of 2013 – *European Urology* (2013).

My research involves the evaluation of risk factors for cancer incidence and cancer progression. The exposures I evaluate are sometimes measured through self-report on questionnaires and sometimes by the measurement of biomarkers, such as levels of a particular substance in the blood or the expression of a genetic marker in tissue. My research often utilizes case-control and cohort study designs, and I oversee both the study design and the statistical analysis of these studies. Based on my education, training, and experience described above, I consider myself to be an expert in cancer epidemiology.

I have never testified as an expert witness in either a deposition or a trial. For my work in this litigation, Hollingsworth LLP is compensating me at $400/hour for literature review and report writing, and $550/hour for deposition and testimony.

II. SCOPE OF THE REPORT

Hollingsworth LLP has requested that I evaluate, from my perspective as an expert in the field of cancer epidemiology, whether there is a body of evidence using population-based research and epidemiologic methods that could demonstrate that glyphosate is a causal factor in the development of non-Hodgkin's lymphoma (NHL).

Attached to this report as Exhibit B, is a Materials Considered List that I relied upon in evaluating the claim for glyphosate being causally related to cancer development. Materials reviewed were those that I deemed to be relevant and appropriate. In

developing this report I have relied extensively on my education, experience, and my knowledge of developments in the field of epidemiology.

III. SUMMARY OF CONCLUSIONS

My conclusions are based on evaluations of individual studies first according to internal validity, followed by precision, and, if warranted, by generalizability. Only one prospective cohort study, the Agricultural Health Study (AHS), has evaluated the effect of glyphosate with respect to NHL and provides a sufficient level of internal validity from which to make any conclusions about causality. With follow up through 2001[1], allowing a maximum induction time between glyphosate exposure and NHL development of 27 years, the analysis was based on 92 cases. Levels of exposure in the highest categories were much greater than in any other published epidemiologic study. Importantly, the study was able to control for other pesticides and conduct dose-response analyses with a large range of exposure levels. The study found no evidence of an increased risk of NHL with use of glyphosate. Concerns about the published AHS analysis, such as the limited number of cases due to the age of cohort participants and limited follow up after enrollment, are addressed by an unpublished update to this analysis that includes 333 NHL cases and an additional 7 years of follow up[2]; this more recent analysis confirmed the original findings of no association between glyphosate and NHL.

All other epidemiologic studies of glyphosate and NHL have been retrospective case-control studies. Given important limitations in study design and analysis, these studies provide a considerably weaker level of evidence than the prospective AHS study. None of the case-control studies identified a statistically significant association between glyphosate and NHL after controlling for other pesticides. Three of these studies were based on very small numbers of exposed cases[3-5], providing too little data to make any determination of causality. Several of the case-control studies have identified statistically significant or suggestive positive associations for NHL not only for glyphosate, but also for nearly all pesticides evaluated. This raises concerns about confounding, selection bias and recall bias [6, 7]. Two North American case-control studies [8, 9] utilize study populations with at most 11 years of glyphosate exposure, but most likely many fewer years of

exposure, such that the cancer cases included in the studies occurred too soon given the latency period for cancer development to be attributable to glyphosate. Moreover, categories of exposure in dose-response analyses were based on very low levels, as little as 2 days per year or 10 days of lifetime exposure in the highest category, which would be reflected in the lowest category of exposure in the AHS study. Therefore, the modest odds ratios identified in case-control studies of glyphosate and NHL without adjustment for other pesticides do not provide evidence of causality.

The North American case-control studies were also incorporated into a pooled analysis, the North American Pooled Project (NAPP)[10-13]. Pooling is an important and potentially informative strategy for studies of rare diseases because it can lead to greater precision of effect estimates and may permit additional subgroup analyses. However, pooling cannot fix bias inherent to the study design of the contributing studies. Unpublished findings from the NAPP adjusted for potential confounders and three other chemicals do not support a causal association between ever use of glyphosate and NHL, nor do they support a dose-response relationship between glyphosate and NHL after adjustment for other chemicals[12].

Given the potential threats to internal validity in the case-control studies, a meta-analysis that attempts to summarize all of the published data could be misleading. In addition, the published meta-analyses of glyphosate and NHL do not include the unpublished data from the AHS or the findings from the NAPP, which plaintiffs' experts agree should be incorporated. These studies would effectively reduce the summary effect estimate in the meta-analyses and render that point estimate no longer statistically significant[14]. Based on the best available evidence from the AHS analyses, there is insufficient epidemiologic evidence to make a scientific conclusion that glyphosate-based herbicides are a cause of NHL.

IV. OVERVIEW OF EPIDEMIOLOGY

According to the World Health Organization, the field of epidemiology evaluates **"**the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems." [15] The specific biologic mechanisms of a disease process may be elaborated in animal and

in vitro studies. However, results obtained from animal models or studies of cells or tissues may not reflect how disease develops in humans. Therefore, epidemiologic studies contribute to the body of evidence required for identifying causal relations between exposures and outcomes in humans.

A challenge in epidemiologic research is that associations between an exposure and a disease or other outcome do not always indicate that the exposure was a *cause* of the disease, which is often the question of interest. We refer to the process of making conclusions about an exposure as a cause of disease as *causal inference.* To evaluate whether a specific exposure, such as glyphosate, causes an outcome, such as NHL, it is useful to consider what outcome a person who was exposed to glyphosate would have occurred if that person had not been exposed to glyphosate, but all other experiences of that person remained exactly the same. This is referred to as the *counterfactual outcome*, and though it cannot be observed directly, the goal of epidemiologic studies is to determine on the population level whether the observed outcome in exposed persons differs from the counterfactual outcome had they not been exposed. As described below, certain aspects of epidemiologic study design and analysis impact whether an association between an exposure and an outcome reflect causation.

A. Types of epidemiologic studies

1. Randomized controlled trials. Randomized, double blind, placebo-controlled, clinical trials are typically considered the study design most conducive to determining causality in humans. Participants are randomly assigned to either an intervention or the control group, which may be a placebo in a trial evaluating drug, or usual care, in a trial evaluating an intervention. Participants are then followed through time for development of pre-specified outcomes. The strength of the association between the exposure and the outcome is measured by comparing the cumulative incidence (i.e., risk) or incidence rate of the outcome in the intervention group and control group with the appropriate measure of association as described below.

If the randomized controlled trial is large enough, randomization provides substantial assurance that all baseline factors (e.g., sex, age, body size, physical activity) are balanced between the intervention and control groups, regardless of whether these

factors are measured. With this study design, a causal relation between the intervention and the outcome of interest in humans can be ascertained because we can assume that the exposed group is interchangeable with the unexposed group for all factors except exposure. Therefore, as long as the participants are analyzed according to the group to which they were randomized (and not according to whether they adhered to the protocol), any difference in outcomes between the two groups would have to be due to exposure.

There are a number of exposures and outcomes that cannot ethically or feasibly be studied in randomized controlled trials. We would never randomize participants to a procedure or substance that we did not believe could potentially be beneficial. However, randomizing participants to a treatment versus standard of care requires a lack of knowledge about whether the new treatment is superior. Similarly, if sufficient evidence of benefit already exists, it would be unethical to withhold the new treatment from the placebo group. In other situations, a randomized controlled trial is not feasible because participants may be unwilling to adopt or maintain a particular behavior to which they are randomized, e.g., long-term calorie restriction or vigorous daily physical activity. When participants do not adhere to the randomized intervention, it will become more difficult to identify a difference in outcomes between the intervention and control groups.

2. Observational studies. In situations where it is impractical or unethical to conduct a randomized controlled trial, epidemiologists use observational studies to obtain human evidence of causality. Observational studies are studies in which the investigators measure exposures that participants experience in their daily lives (e.g., level of physical activity, consumption of particular foods, medication use, etc.) and then ascertain disease outcomes. Analytic observational studies, which include cohort studies and case-control studies, utilize a control group in order to compare the occurrence of an outcome in an exposed group to the occurrence of the outcome in a comparable group not exposed. These studies may enable investigators to conclude there is an association between the exposure and outcome of interest, but typically cannot confirm that the exposure *causes* the outcome, even in well-designed studies, because of the potential for unidentified biases or inadequately controlled confounding (described below).

Cohort studies are similar to randomized controlled trials in that that they begin with a group of exposed and unexposed individuals who have not yet developed the outcome of interest (i.e. *at risk* for the outcome) and collect information on prior exposure before development of disease. In observational cohort studies, however, the exposure is not assigned by the investigators, but reflects the natural experience of the participants. Cohort studies are forward looking (prospective) in that participants are followed through time until the occurrence of disease or the end of the study, allowing direct estimation of the cumulative incidence or incidence rate of disease in exposed and unexposed groups. Reporting of exposure cannot vary by disease status, because disease has not yet occurred at the time exposure information is collected. Especially for studies that require very long periods of observation between exposure and disease, investigators often have to put in place safeguards against loss to follow up, which may occur because participants are no longer interested in being a part of the study or because they relocate. These could include attempts to contact questionnaire non-responders with reminder cards, follow-up telephone calls, additional distribution of mailed questionnaires, as well as use of registries to collect information on primary study outcomes to facilitate outcome information collection even among non-responders.

In *case-control studies*, the investigator sets the number of diseased and non-diseased individuals at the outset of the study. Epidemiologists often use the case-control study when cohort studies are too time consuming, too expensive, or otherwise not feasible. For example, when the disease of interest is rare or there is a long delay between exposure and disease diagnosis, a very large cohort study with long-term follow up would be required to observe a sufficient number of disease events. Case-control studies can be more efficient, but there is a trade-off in terms of potential threats to validity. The vast majority of case-control studies are retrospective, that is, information on exposure is collected *after* the development of the outcome[i]. In fact, all of the glyphosate case-control

[i] An exception is nested case-control studies (not utilized in glyphosate epidemiology studies), which are case-control studies conducted within a well-established cohort. Investigators might collect blood specimens or other biological specimens on the entire cohort, but wait to analyze certain biomarkers until after a sufficient amount of follow-up for the disease to occur. Measurement of the biomarkers in these cases and controls would then be prospective, because the exposure predated the development of disease.

studies are retrospective. In retrospective case-control studies where cases (or their proxies) and controls are asked to provide information about past exposures, *recall bias* can occur (described below).

Although case-control studies are often conceptualized as a comparison of diseased and non-diseased individuals, this view often leads to problems in study design, analysis and interpretation. Case-control studies should instead be viewed as an efficient means of sampling from an underlying cohort, with the purpose of the controls being to represent the distribution of exposure in the study base from which the cases were drawn. If the included controls do not reflect the distribution of exposure in the underlying source population, selection bias can occur (described below). Although analyses could be undertaken to determine the potential impact of selection bias on the observed measure of association given hypothetical assumptions, there is no way to ameliorate selection bias at the analysis stage once it has occurred.

3. Measures of association provide a way to describe the magnitude of the association between exposure and an outcome. Relative measures, which were used for all epidemiologic studies of glyphosate and NHL, involve dividing the chance of developing the outcome event in the exposed group by the chance of developing the outcome event in an unexposed group. Relative measures may include risk ratios, rate ratios (i.e., hazard ratios), and odds ratios. A ratio less than 1 indicates that exposure is less common among those who are diseased (i.e., negative association), a ratio of 1 is a null finding (i.e., no association), and a ratio > 1 indicates that exposure is more common among those who are diseased (i.e., positive association). Sometimes the term “relative risk” is used to encompass all of the relative measures of association. In general, the study design determines which types of measures of association can be estimated.

3.1 Risk ratios

Risk ratios (also referred to as cumulative incidence ratios) can be estimated from cohort studies. At the beginning of the study, participants are divided into exposed and unexposed. Both groups are followed through time. At the end of follow up, the risk in the exposed is calculated as the proportion of the exposed group that develops the

outcome. The risk in the unexposed group is calculated as the proportion of the unexposed group that develops the outcome. These two quantities can then be divided to obtain the risk ratio.

3.2 Rate ratios

Rate ratios are also estimated from cohort studies. Rate ratios are calculated similarly to risk ratios, but instead of the denominator of the exposed and unexposed groups including numbers of people, the denominator is now exposed and unexposed *person-time*. For instance, one person followed for 12 months would contribute 12 person-months to the denominator. Equivalently, 12 people followed for one month would also contribute 12 person-months to the denominator. Dividing the number of events in the exposed group by the person-time in the exposed group provides the incidence rate in the exposed. This could be divided by the incidence rate in the unexposed to estimate the incidence rate ratio. Unlike the risk ratio, this measure of association takes into account the variable follow up of cohort members, and is therefore more appropriate when some subjects are lost to follow up prior to the end of the study or die of other causes before they have an opportunity to develop the outcome of interest. This is especially important for the study of diseases that require very long follow up, such as cancer. Statistical models including Poisson regression models and Cox proportional hazards models provide rate ratio estimates and can be used to control for other variables.

3.3 Odds ratios

Odds ratios are the measures of association estimated from case-control studies. In case-control studies, the investigator determines the number of participants with and without the outcome, which prohibits the estimation of risk or rates directly. Instead, the odds of exposure in the cases (i.e., those who develop the outcome) are compared to the odds of exposure in the controls. Odds are the probability of the exposure divided by 1 minus the probability of exposure. Conveniently, the exposure odds in the cases divided by the exposure odds in the controls is algebraically equivalent to the odds of disease in the exposed divided by the odds of disease in the unexposed. As a result, the odds ratio

can be used as a relative measure of association to describe the increase or decrease in chances of the outcome associated with exposure. Odds ratios can be estimated from logistic regression models in order to control for other variables.

B. Analysis and interpretation of epidemiologic studies

The point estimate for an association must be interpreted first in the context of internal validity (the impact of potential bias); second with respect to the precision of the estimate (the range of results that are likely to be consistent with the data given study size); and third in terms of whether the results can be generalized to other groups or populations (external validity). A study that is flawed in design will produce a point estimate that is biased and does not reflect the underlying relationship between exposure and disease. As a result, there is no value in discussing the precision around this estimate or its generalizability. If a point estimate is valid, in that it is free from bias, but the study is small and the confidence intervals are very wide, there would be concern that the results were simply due to chance (i.e., random error). Only after there is confidence in both the validity and the precision of the results is it necessary to think about whether the results would be generalizable to groups of individuals not studied.

1. Threats to internal study validity.

Confounding factors are other causes of the outcome of interest that are associated with the exposure that could create a non-causal association of the exposure with the outcome. For example, studies have reported that farmers have higher rates of some types of cancer than nonfarmers (as described in more detail below), including studies conducted before the introduction of glyphosate into the market. While a specific causal agent has not been identified, these studies indicate farmers may differ from non-farmers in ways that might also be related to a higher risk of cancer. Farmers and non-farmers could differ on dietary or lifestyle factors, use of certain medications, occupational exposures, or even family history. Therefore, if we compare an exposure that is more common in farmers than in non-farmers to the risk of developing cancer, the exposure may appear associated with cancer simply through its association with farming. Thinking about it another way, a group of farmers exposed to glyphosate may develop NHL, but

the (unobserved) counterfactual outcome among those same farmers when not exposed to glyphosate is also development of NHL. In this example, glyphosate does not have any impact on the development of NHL, and is therefore not the *cause* of NHL, but could be associated with NHL in an epidemiology study.

Studies conducted only among farmers could reduce potential confounding by exposures related to farming. However, if there are dietary, lifestyle, or other occupational factors that are associated with glyphosate and NHL risk among farmers that are not controlled for in the analysis, which is more likely to occur in the study of a disease with an unknown etiology, confounding could create an association that is not reflective of causation. Cohort and case-control studies are prone to bias from confounding because exposed individuals may differ from unexposed individuals with respect to risk of the outcome in ways other than just the exposure. The control of confounding requires that information on potential confounders be collected and measured accurately enough to permit adjustment at the time of statistical analysis. While epidemiologists can use strategies at the study design phase or during statistical analysis to control for known confounders, the same is not true for unknown confounders. This point is especially relevant to NHL studies, as the possibility for unknown confounding is high given approximately 53% of NHL derives from unknown risk factors (discussed below).

As shown in the following 2 x 2 tables, an apparent association between an exposure and disease can actually be due to a third variable that is associated with exposure and disease. If that variable is not considered in the analysis, one may erroneously conclude that exposure causes disease. However, once you separate or "stratify" the data into categories of the third variable, thereby removing any variability in that variable within each stratum, the association between exposure and disease observed initially disappears.

Below is a classic example of confounding of the male gender and malaria development by outdoor occupation[16]. The crude data ignoring information on outdoor occupation are presented below:

	Malaria cases (N=150)	Controls (N=150)
Males	88	68
Females	62	82
Odds ratio: 1.71		

The unadjusted (crude) odds ratio for the association between male gender and malaria is 1.71, indicating that men have 1.71 times the odds of malaria compared to females. However, we now stratify by outdoor/indoor occupation. The stratified data are as follows:

Outdoor occupation		
	Malaria cases	Controls
Males	53	15
Females	10	3
Odds ratio: 1.06		

Indoor occupation		
	Malaria cases	Controls
Males	35	53
Females	52	79
Odds ratio: 1.00		

In the stratum of participants with an outdoor occupation, the odds ratio for the association between male gender and malaria is 1.06, indicating a very weak or null association. In the stratum of participants with an indoor occupation, the odds ratio for the association between male gender and malaria is 1.00, indicating no association. The discrepancy between the crude odds ratio and the stratum-specific odds ratios occurs because outdoor occupation is associated with the exposure, male gender, and with the

outcome, malaria. In the study population, men were much more likely to have outdoor occupations. Having an outdoor occupation is strongly associated with developing malaria because it creates the opportunity to be exposed to malaria-infected mosquitos. Therefore, without adjustment for outdoor occupation, the crude association between male gender and malaria was confounded.

In randomized controlled trials of a large enough size, randomization of exposure will ensure that there is no association between exposure and both measured and unmeasured variables, and therefore no confounding by measured or unmeasured variables. In all observational studies, confounding is a threat to validity unless adequately addressed at the study design and/or analysis stage.

Misclassification is the imperfect measurement of the exposure or the outcome and represents another threat to study validity. An exposure may be misclassified because of reliance on a participant's memory of past events. The exposure may also be improperly specified because it is measured at the wrong time point in terms of the etiology of disease. For instance, in determining whether mayonnaise was associated with the onset of a gastrointestinal illness, classifying participants as exposed if they had consumed mayonnaise 6 months ago would improperly characterize the exposure. The meaningful exposure would have occurred within hours or days before the illness. For a disease with a long induction time, such as skin cancer, sun exposure on one day does not produce a detectable tumor on the next day. Any association we observed between sun exposure on one day and skin cancer on the next day would be due to confounding, bias, or chance. The period between exposure and disease development, also called the latent period, is an important consideration in designing and conducting a study.

Exposure misclassification that is non-differential with respect to outcome (i.e., diseased and non-diseased persons have the same errors in reporting of their exposure) can occur in cohort studies and case-control studies. In general, non-differential misclassification of the exposure tends to make the results appear more conservative than in truth. The predictability of the direction of the bias can be utilized when interpreting study results, because the observed finding would tend to underestimate the true underlying association. However, in the presence of confounding and other biases, the observed association may still be an overestimate of the true association, even in the

presence of non-differential misclassification of exposure. Moreover, there are certain situations when exposure levels are divided into three or more categories, such as in analyses of dose response, where misclassification in specific categories can lead to bias away from the null, overestimating the true association.

Recall bias exists when the quality of exposure information differs between cases and controls, such that the obtained effect estimate can overestimate the true effect. In case-control studies, participants are aware of their disease status when they report exposure. If cancer patients who are searching for the causes of their disease are more likely to over-report having been exposed to a certain risk, an exposure will look more strongly associated with the disease than in truth. This type of over-reporting in cases is of particular concern when participants are told about the exposure-outcome relationship under study or if they are able to infer the study hypothesis given the types of questions included in a questionnaire.

Put differently, recall bias results when the ability to correctly classify exposure differs in the diseased and non-diseased. The hypothetical data from a case-control study illustrate how recall bias can bias the results of a study so that they appear stronger than in truth. Consider the following "true" distribution of exposure in cases and controls:

	Cases (N=100)	Controls (N=100)
Exposed	50	50
Unexposed	50	50
Odds ratio: 1.0		

If we were able to perfectly classify exposure, we find an odds ratio of 1.0 indicating a null association. However, now consider the case of misclassification of exposure, or recall bias. All of the participants who were unexposed correctly report that they were unexposed. However, 96% of the exposed cases correctly report their exposure, but only 70% of the exposed controls correctly report their exposure. In other words, there is more severe under-reporting of exposure in the controls, which results in the following data being collected:

	Cases (N=100)	Controls (N=100)
Exposed	48	35
Unexposed	52	65
Odds ratio: 1.7		

Recall bias leads to an odds ratio that is spuriously inflated to 1.7. Unless we knew the degree to which cases and controls misreported exposure, which is typically not possible, we cannot correct for recall bias. There are, however, methods to examine the potential impact of recall bias on the results hypothetically.

Unlike case-control studies, cohort studies are not subject to recall bias. In cohort studies, the collection of information on exposure happens *before* the participants develop disease. Therefore, if errors in reporting of exposure information occur, they usually occur at the same rate in those who do and do not later develop the outcome.

The use of biomarkers of exposure in population-based studies represents one way to avoid the problems of misclassification of self-reported exposures. None of the epidemiologic studies of glyphosate and NHL utilize this approach. For instance, a study that wishes to evaluate the association between selenium and cancer risk could evaluate selenium levels from toenail clippings, which are known to reflect exposure in the prior 3-12 months. Rather than estimating vitamin D exposure from self-reported diet and sun exposure, 25(OH)-vitamin D levels could be measured in the blood. Biomarkers also have the advantage of representing exposure in terms of an internal dose, which may be more relevant for disease development than an external dose. In the Acquavella *et al*. 2004 study[17], pesticide applicators were evaluated for the presence of glyphosate in urine on the day of pesticide application. Only 60% were found to have detectable levels of glyphosate in urine on the day of application. The use of gloves was associated with having lower or undetectable levels. However, levels in all applicators were universally below the U.S. Environmental Protection Agency reference dose level. These data indicate that self-reported exposure to glyphosate is not a reflection of the amount of glyphosate in the body. In addition, these results point to the importance of collecting

detailed information on specific application practices, such as the use of protective equipment, in determining exposure.

Selection bias results from the analyzed group of study participants not being representative of the underlying study population. Selection bias can occur in both cohort and case-control studies. While there are numerous names for selection bias depending on the specific scenario (healthy worker bias, volunteer bias, informative censoring, non-response bias, differential loss to follow up, etc.), a unifying concept is that selection bias involves restricting the analysis based on another factor that is a common cause of both the exposure and the outcome[18]. As a result, an association between exposure and outcome can be observed even if no causal association exists. In cohort studies, selection bias can occur, for instance, when participants self-select out of a study or because certain data required for analysis is missing. In both cases, the analyzed sample does not reflect the intended population under study.

Case-control studies are particularly prone to selection bias because, by definition, selection into the study is based on disease status. The investigator determines the number of participants who are diseased and non-diseased. Therefore, if selection into the study or voluntary participation is also based on exposure status, selection bias can occur. This happens when controls are inappropriately selected and do not reflect the exposure distribution of the underlying cohort from which the cases were sampled. For instance, if we consider the study base to be all farmers living in Iowa, the controls we select should have the same distribution of exposure as all farmers living in Iowa. If we randomly invite controls sampled from the entire population of farmers in Iowa, these controls should have the same exposure distribution as the entire population of Iowan farmers. However, if the response rate for controls is only 50%, there is a much greater likelihood that the farmers who elect to participate will not be representative of the entire population of Iowan farmers in terms of their exposure distribution. Therefore, low response rates in the controls raise greater concern about selection bias. Sometimes selection bias can occur at the analysis stage when the investigators exclude participants from analysis. Selection bias can make the study results appear either stronger or more conservative than in truth.

2. Precision of the estimate.

Confidence intervals illustrate the precision or lack of certainty around a particular measure of association (e.g., RR: 1.1; 95% CI: 0.7-1.9). When interpreting confidence intervals, we must first assume that the study be free from confounding and systematic bias. Therefore, a forest plot of all confidence intervals and point estimates obtained from various studies without respect to control for potential confounders and other biases, such as the plot shown on page 14 of the plaintiffs' expert report by Dr. Ritz, can misrepresent the evidence. Confidence intervals can be interpreted in terms of repeated studies of the exposure and disease of interest. If a study were repeated 100 times, 95 of the studies would yield a 95% confidence interval that included the true value of the association; 5 of the studies would not include the true value of the association within the confidence interval. When the confidence interval for a relative measure of association (such as the rate ratio or odds ratio) from a single study contains the null value of 1, the finding is consistent with there being no association between the exposure and outcome, and is generally considered a non-statistically significant finding.

We are much more likely to identify a confidence interval that does not include the null value if we increase the number of statistical tests that we are performing. This is often referred to as a problem of multiple comparisons. There are ways to correct for multiple comparisons in order to avoid over-interpretation; another strategy would be to report more strict confidence limits, such as 99% confidence intervals, as I did in a study of 99 genetic markers and prostate cancer risk in an exploratory analysis[19]. The 99% confidence intervals for associations of glyphosate and NHL would be even wider than the 95% confidence intervals reported in all of the prior studies. For instance, in a case-control study of 500 cases and 500 controls and an odds ratio of 1.65, the 95% confidence interval is (0.90-3.01) and the 99% confidence interval is (0.75-3.63).

Study power. The number of exposed individuals with the outcome of interest contributes to the power of a study. The table on page 15 of Dr. Ritz's report that orders the studies by the number of cases and controls could lead one to believe that the study by Cocco *et al.*[5] is the most statistically powerful study of glyphosate and NHL. In reality, that study was based on just 4 exposed cases and 2 exposed controls, and is one of the weakest studies, reflected in its very wide confidence intervals (95% CI: 0.6-17.1).

In addition to ensuring an adequate distribution of exposure, greater certainty around the results of a case-control study can be obtained by sampling additional controls per case. For instance, a case-control study with 2:1 matched controls will typically provide more precision in estimates than a study with 1:1 matched controls. At a certain point the gains in efficiency with additional controls begin to level off, but this point depends on the strength of association between the exposure and outcome, which is usually unknown at the study outset. Cohort studies are often designed to have an approximately equal number of exposed and unexposed persons and a follow up of sufficient length to obtain an adequate number of events. Large, adequately powered studies also have the advantage of allowing the investigation of exposures with more categories (e.g., when measuring coffee intake, categories might consists of 0 cups per day, 1-2 cups per day, 3-6 cups of coffee per day, and >6 cups per day) or the evaluation of particular subgroups of outcomes that are more relevant in terms of the true underlying association between exposure and disease (e.g., subtypes of NHL or cases that satisfy a minimum latency period between exposure and disease).

Pooled analyses and meta-analyses have overlapping but somewhat distinct purposes and goals. Pooled analyses take the primary data from previously conducted studies and combine it to allow for analyses with greater precision. Pooled analyses rely on the quality of the original data collected from each individual study; flaws in study design in the original study, leading to problems with internal validity, will carry forward into the pooled study. However, because pooled analyses represent a re-analysis of the original data, they do allow for decisions to be made about the type of statistical analysis undertaken and the other variables that can be controlled in an analysis, as long as those variables were collected. Pooled analyses are often the only way to obtain statistically precise results from observational studies of rare diseases.

Meta-analyses do not re-analyze primary data obtained from the original study. Meta-analyses simply combine the measures of effect obtained from previous studies and weigh them according to study size and the width of the confidence intervals. Sometimes subgroups of studies will be separately considered according to, for instance, cohort or case-control study design. Any limitations of both the study design and statistical analysis of included studies carry forward through the results of the meta-analysis. Therefore,

interpretation of the results of a meta-analysis must take into account any systematic bias in the design and analysis of the individual contributing studies. Moreover, publication bias can profoundly influence the results of a meta-analysis. Both the decision to publish results and the results that are incorporated into a publication can influence the evidence that is readily available for inclusion in a meta-analysis (Blair *et al.*, 1995), and selective publication typically overestimates the effect estimate (Blair *et al.*, 1995; Stroup *et al.*, 2000). As pointed out by Blair *et al.* (1995), publication bias "usually tends to push results in a positive direction (i.e., in the direction of increased risk)." Similarly, Blettner *et al.* (1999) stated in their review article:

> Meta-analysis of published papers has several severe limitations. One limitation is that publication bias is particularly important in epidemiological research since some analyses may be done in a very exploratory way and may be only published selectively. As mainly unexpected significant results may be selected for publication, an overestimate of the risk estimate is likely. (page 2)

To ameliorate publication bias, both Blair *et al.* and Blettner *et al.* recommend incorporating unpublished data into the meta-analysis if that data meets other selection criteria. Sometimes this will require directly contacting the study investigators to obtain relevant results. While meta-analyses that include all relevant results could aid in synthesizing existing data, they are not substitutes for large, thoughtfully conceived prospective studies, especially when the included studies are flawed.

3. Generalizability.

Only after all potential threats to internal study validity have been evaluated should the generalizability of a study be considered. Generalizability, or external validity, refers to the ability of study results to be applied to other groups or populations. For instance, one might ask whether the results of a study in men could be generalized to women, or a study in farmers could be generalized to non-farmers. Generalizability is closely tied to the concept of biologic interaction. Oftentimes the association between an exposure and an outcome varies according to the presence of a third variable. For instance, the association between smoking and lung cancer is much stronger in certain occupational groups, namely patients also exposed to asbestos, than in patients not exposed to asbestos. Results of a study are generalizable unless one believes that there is biologic

interaction. For instance, a study of aspirin and cardiovascular disease in men could be generalized to women unless one believed that the underlying biologic association between aspirin and cardiovascular disease varied by sex.

V. EPIDEMIOLOGY OF NON-HODGKIN'S LYMPHOMA

NHL is comprised of a diverse group of distinct malignancies of the blood. In the United States, approximately 85% of NHL is comprised of B-cell lymphomas. B-cell lymphomas can be further divided into histological subtypes including Diffuse Large B-cell Lymphoma (DLBCL), the most common form of NHL in the US; follicular lymphoma; chronic lymphocytic leukemia and small lymphocytic lymphoma; mantle cell lymphoma; marginal zone B-cell lymphomas; Burkitts lymphoma; hairy cell lymphoma; and primary central nervous system lymphoma. T-cell lymphomas as a group are more rare and are comprised of precursor T-lymphoblastic lymphoma/leukemia and various peripheral T-cell lymphomas[20]. All of these diseases are considered to be distinct with unique etiologies and response to treatment[21]. Therefore, epidemiological studies could be more informative if they considered subtypes when seeking to identify novel risk factors.

For the last decade, the incidence of NHL has been decreasing by an average of 0.6% per year[22]. Steadily rising rates of 3-4% per year were observed from the mid-1970s to the early 1990s in the U.S. and other developed countries. While AIDS-associated NHL incidence is partly responsible, non-AIDS-related NHL also rose during this period. One estimate suggests that after accounting for all known risk factors, 53% of the increase in NHL risk is still unexplained[23]. One challenge in trying to understand the source of increases in incidence is the long latency period between a causal exposure and disease, as the causal exposure likely predated the increase in disease incidence by decades. The paucity of known risk factors for NHL also makes it more challenging to avoid unmeasured confounding in observational studies aimed at identifying novel risk factors.

<u>Known or suspected risk factors</u>

While there appears to be a genetic component of NHL risk, other diseases and environmental exposures also contribute to risk. NHL overall is more common among males than females and more common in whites compared to blacks for most subtypes. Risk increases steadily with age. Autoimmune diseases including Rheumatoid arthritis, systemic lupus erythematosus and celiac disease are all associated with increased NHL risk. Many other risk factors appear to vary across the individual NHL subtypes. For instance, Burkitts lymphoma is strongly associated with Epstein-Barr virus infection and is also more commonly diagnosed in immunosuppressed persons including those with HIV. Human T-cell leukemia/lymphoma virus is an established cause of adult T-cell leukemia/lymphoma. Ultraviolet radiation and other forms of immune suppression including transplant, as well as hair dyes, and dietary factors have been repeatedly implicated in NHL generally or in more common subtypes.

Farming and agricultural exposures have long been suspected as potential NHL risk factors, even before the availability of glyphosate, and some of these studies have found suggestions of increased risk. For instance, in a case-control study using death certificates in Ohio during the years 1958-1973, Dubrow *et al.* [24] found that the association between farming occupation and NHL was 2.1 (95% CI: 0.9-4.8). In a cohort study in Saskatchewan[25], the rate ratio for NHL comparing the highest category of exposure for spraying of herbicides in 1970 (prior to glyphosate) compared to no exposure was 2.2 (95% CI: 1.0-4.6). However, most of the more recent studies evaluating specific occupational risk factors for NHL have been retrospective and have relied on self-reported exposure histories. Because there is likely a long induction period between exposure and NHL development, this approach requires an accurate assessment of exposure histories in the very distant past.

VI. ANALYSIS OF THE AVAILABLE EPIDEMIOLOGIC EVIDENCE REGARDING THE EFFECT OF GLYPHOSTATE-BASED HERBICIDES ON NON-HODGKIN'S LYMPHOMA

A. Introduction

At a minimum, a reliable epidemiologic study of glyphosate and NHL would be prospective and allow for an induction/latent period (i.e., the interval between exposure and detectable disease) of at least a decade; be adequately powered for identifying associations with individual NHL subtypes; capture etiologically relevant exposure measurement in terms of timing of exposure and intensity of exposure to permit analyses of dose response, potentially through the use of a biomarker; and collect data on potential confounders including other pesticides.

While multiple case-control studies and one large prospective cohort study relating glyphosate exposure to NHL incidence have been published, confounding and other forms of systematic bias cannot be ruled out in these studies. Importantly, **none of the studies identified a statistically significant association between glyphosate and NHL after adjustment for other pesticides**. The only statistically significant associations identified were in unadjusted or minimally adjusted analyses. In fact, many of these studies did not identify a statistically significant association in analyses adjusted only for age, race and geographic region. Given that there are few known risk factors for NHL, the potential for unmeasured confounding is high[ii]. More specifically, exposures related to farming could confound the association between glyphosate and NHL. One of these potential confounders is the use of other pesticides and agricultural chemicals. For example in the Eriksson *et al.* 2008 study[6] and McDuffie *et al.* study[7], nearly all chemicals evaluated were associated positively with NHL in analyses unadjusted for other pesticides. This phenomenon could be explained by a systematic bias including one or all of the following: i) an unmeasured confounder associated with exposure to all evaluated chemicals; ii) selection bias; or iii) recall bias.

B. Cohort studies

De Roos *et al.* 2005[1]

Study Design. The only prospective cohort study evaluating glyphosate and cancer incidence published to date is the Agricultural Health Study (AHS). This U.S.

[ii] The Swedish case-control studies of glyphosate and NHL generally do not include a table listing the distribution of potential confounding factors stratified by either disease status or exposure status, making it difficult to evaluate the potential for confounding by measured variables.

government-funded study included 57,311 licensed pesticide applicators residing in Iowa and North Carolina recruited between 1993-1997. An enrollment questionnaire and baseline supplemental questionnaire asked about exposures prior to baseline such that an exposure as early as 1975 could have been captured. The study collected detailed data on usage patterns of 22 pesticides, as well as ever/never use of an additional 28 pesticides. Of all participants, 75% used glyphosate. Reminder postcards, telephone calls, and an additional questionnaire mailing were used for non-responders. Exposure was categorized as ever vs. never use, as well using methods to capture dose response including cumulative lifetime days and intensity-weighted cumulative exposure. The study followed participants through 2001 for development of NHL. Annual linkage with state cancer registries and the National Death Index was conducted to obtain outcome data. A total of 2,088 total cancers were diagnosed, of which 92 were determined to be NHL. The authors used Poisson regression[iii] to estimate the incidence rates of cancer overall, as well as the incidence rates for specific cancer types.

Results. In general, participants were long-term glyphosate users with a much higher level of exposure than in previous case-control studies (tertiles of 1-20, 21-56, and 57-2,678 cumulative lifetime exposure days). Glyphosate users were very likely to be users of other chemicals. The study rate ratio for the association between ever vs. never use of glyphosate and NHL in age-adjusted analyses was 1.2 (95% CI: 0.7-1.9). The rate ratio for NHL in multivariable-adjusted analysis, including adjustment for other pesticides, was 1.1 (95% CI: 0.7-1.9). The results found no evidence of a dose-response relationship between glyphosate and NHL, as indicated by every dose-response measurement outlined below. Compared to participants reporting 1-20 cumulative lifetime days of exposure, the rate ratios for NHL with 21-56 and 57-2,678 cumulative lifetime days of exposure were 0.7 (95% CI: 0.4-1.4) and 0.9 (95% CI: 0.5-1.6), respectively, with no statistically significant trend across tertiles. In analyses that also incorporated the intensity of glyphosate exposure[iv] into the cumulative number of exposure days, the individual rate ratios comparing the second and third tertiles to the first tertile of exposure and the lack

[iii] Poisson regression is a commonly used approach for modeling counts of events that occur over time.

[iv] Exposure intensity was incorporated based on mixing status, application method, equipment repair status and use of personal protective equipment

of statistically significant trend across tertiles were consistent with no association; the rate ratios for tertiles 2 and 3 were 0.6 (95% CI: 0.3-1.1) and 0.8 (95% CI: 0.5-1.4), respectively.

Internal validity. To follow up on hypothesis-generating results from prior case-control studies of glyphosate and NHL, a prospective cohort study is the preferred study design. Strengths of the AHS include the general advantages of cohort studies over case-control studies, including the ability to evaluate temporality; amelioration of concerns about recall bias (i.e., differential misclassification of exposure); and the avoidance of selection bias resulting from inappropriate control selection. Exposure was assessed at only one time point, but other studies have indicated reliable reporting of pesticide use by farmers[26-29]. We would expect the quality of reporting to be at least as accurate as in the case-control studies where recall bias may have played a role. The AHS employed a number of safeguards to minimize missing data on the exposure and loss to follow up, including regular reminders about study participation and second questionnaire mailings, as well as utilization of state/national registries for outcome information. Exclusions due to missing data on ever use of glyphosate (1,678; 2.9% of the cohort) or loss to follow up (298; 0.5% of the cohort) were modest. Moreover, analyses of cumulative exposure days and intensity-weighted exposure days were based on a more limited group of participants with complete data. Cumulative exposure was based on 36,823 participants in partially adjusted models and 30,699 participants in models fully adjusted for other pesticides. For missing data to lead to bias, participants who reported ever use of glyphosate but failed to complete questions related to duration or intensity of glyphosate use would need to differ from those who completed all of the questions on glyphosate with respect to both the duration/intensity of glyphosate use and the subsequent likelihood of being diagnosed with NHL. For the resulting rate ratio to be an underestimate of the true causal association, non-responders would need to be more likely to be exposed to higher doses of glyphosate and more likely to develop NHL during study follow up. However, there is no reason to believe that more frequent users of glyphosate would be less inclined to answer additional questions about their exposure, or that non-responders would have a higher risk of NHL.

In the dose-response analysis accounting for lifetime exposure days and intensity-weighted exposure, the range of exposures evaluated in this study is many orders of magnitude greater than those evaluated in the case-control studies. The AHS was able to collect cumulative exposure days and intensity-weighted cumulative exposure for up to 26 years, allowing up to 2,678 exposure days. The exposed were grouped into tertiles rather than dichotomized at the median as in the case-control studies. If a dose-response relationship exists, we would be much more likely to observe that trend in the AHS study than in studies where the exposure was dichotomized at 2 days per year or 10 lifetime days. Moreover, the AHS analysis included a test of trend across categories to formally test the hypothesis that rates of NHL increased as glyphosate dose increased.

The major limitation of this study relates to the investigators' decision to "let the sample size float" between age-adjusted and multivariable adjusted analyses. The age-adjusted analyses included 54,315 participants, but the multivariable analysis was restricted to 40,719 participants with complete data. While further covariate adjustment did not appreciably influence results for NHL, an increase in OR from 1.1 (95% CI: 0.5-2.4) to 2.6 (95% CI: 0.7-9.4) for multiple myeloma suggests potential problems in the comparability of the results from the two models. If the restricted sample is not representative of the entire cohort with respect to the distribution of glyphosate and NHL, selection bias would occur in the multivariable analyses. In fact, the occurrence of this phenomenon is supported by a re-analysis of the data by Sorahan[30] based on the outcome of multiple myeloma that used the full dataset in fully adjusted models including lifestyle factors and other pesticides. Unlike the suggestion of a positive association for multiple myeloma reported by De Roos *et al.*, Sorahan found a rate ratio of 1.24, very similar to the minimally adjusted findings. Therefore, while the interpretation of the results of the multivariable-adjusted analysis in De Roos *et al.* is limited, there is no reason to believe that selection bias in the original analysis yielded a result that was an underestimate of the true association. While we can never completely rule out the possibility of unmeasured confounding, collection of information on other occupational and lifestyle variables was extensive and minimizes this concern. Although exposure was common and levels of exposure were high, secondary analyses assuming specific disease latency periods were not performed.

Precision. The confidence intervals adjusted for other pesticides for ever vs. never use of glyphosate (RR: 1.1; 95% CI: 0.7-1.9) are the most precise in the published literature. For AHS analyses of dose response using cumulative exposure days, in which the middle category of exposure represents a higher level than in the Eriksson *et al.* study, confidence intervals are also at least as precise (95% CI for 21-56 days: 0.4-1.4; 95% CI: for 57-2,678 days: 0.5-1.6) even when controlling for use of other pesticides.

Alavanja *et al.*, 2013 (unpublished draft)[2]

Study Design. While not yet published, a draft manuscript that includes follow up of the AHS through 2008, allowing a maximum induction time between glyphosate exposure and NHL development of 34 years, is also available. This draft was subsequently published in revised form but the glyphosate data was omitted[31]. The study design and methods are generally similar to the study published in 2005[1]. The updated analysis includes 320 NHL cases with glyphosate data[v], which represents the largest study to date. While the 2005 publication used exposure information obtained only from the baseline/enrollment questionnaires, the more recent analysis incorporates data from a follow-up questionnaire that was distributed between 1998-2003 and completed by 63% of the enrolled cohort in order to obtain information on more recent exposure. For follow-up survey non-responders, more recent exposure values were imputed. In dose-response analyses, the reference group included those with no exposure, rather than those in the lowest tertile of exposure as in the De Roos *et al.* 2005 study[1]. In addition to analyses for all NHL, the four major categories of NHL were also analyzed as distinct outcomes. Sensitivity analyses were performed to explore the impact of the additional follow-up questionnaire data, as well as lagging exposure by 5 or 15 years given that exposure close to the time of NHL diagnosis likely does not influence disease development. However, results from lagged analyses are not included in the manuscript draft.

Results. With even higher levels of cumulative exposure than in the 2005 study, the rate ratios for tertiles of cumulative exposure days of glyphosate compared to no

[v] The 333 NHL cases reflect an update to the classification of NHL that occurred following the original 2003 publication. The authors provide analyses of all 320 cases with glyphosate data, as well as analyses based on 231 cases consistent with the previous NHL definition. Findings are the same regardless of case definition.

exposure were 0.8 (95% CI: 0.6-1.2), 0.8 (95% CI: 0.6-1.2), and 1.0 (95% CI: 0.7-1.4), respectively, in fully adjusted models. For intensity-weighted cumulative exposure, the rate ratios for tertiles 1, 2, 3 when compared to no exposure were 0.9 (95% CI: 0.6-1.3), 0.8 (95% CI: 0.5-1.1), and 1.0 (95% CI: 0.7-1.4), respectively. Sensitivity analyses indicated that results were similar when follow-up questionnaire results were excluded and the prior definition of NHL was used.

Internal validity. Strengths of the updated analysis include the even longer latency period and the older age of participants, resulting in a substantial number of additional cases accrued during follow up between 2001 and 2008. The updated analysis of glyphosate has not been published in a peer-reviewed journal. Nonetheless, given that publications using data from the same cohort have undergone peer review and that the analysis methods remain largely similar to the published 2014 manuscript[31], the unpublished findings in this established cohort study are likely more reliable than in a novel study that has not yet been subjected to peer review.

Exposure information for the primary analyses of lifetime days of glyphosate use and intensity-weighted lifetime days of use incorporated questionnaire data from the baseline questionnaires and a follow-up questionnaire. For participants who did not complete the follow-up questionnaire (37%), an imputation strategy was used to assign updated exposure status based on other available information. Given that this degree of missing data could lead to selection bias and influence the results, the authors conducted a sensitivity analysis where they only included exposure information from the baseline questionnaires. While the estimates using only baseline data were less precise, they were of a similar magnitude as the estimates that used imputation, providing evidence that selection bias was not a threat to validity. A separate analysis within the AHS cohort undertaken to determine the potential impact of selection bias given non-response to the follow-up questionnaire for updated exposure information provides additional reassurance that the results obtained would not differ substantially from those obtained in the full cohort (Rinsky *et al.*, Am J Epidemiol 2017). In that analysis, the authors found that for an exposure that is only weakly associated with questionnaire response, which includes pesticide application, response to the questionnaire had to be very strongly related to the specific cancer endpoint in order for bias to meaningfully impact the results

in an analysis restricted to respondents. Therefore, the approach for handling missing data in this analysis appears appropriate and unlikely to have led to biased results.

Precision. In the analysis with follow up through 2008 including 320 NHL cases, the largest study to date, but also in the analysis of 231 cases consistent with the prior definition of NHL, confidence intervals for the dose response also suggest a good degree of precision around the estimates.

C. Case-control studies

1. Swedish Case-Control Studies

All three of the Swedish studies share important limitations. Some of these limitations are inherent in the study design (e.g. potential for recall bias in a retrospective case-control study); some reflect the challenges of conducting a population-based study of a rare outcome and exposures that are highly correlated; and others involve choices made during study design and analysis. Two of the studies are too small in terms of the number of exposed cases and controls to provide results that are interpretable causally. All three studies identified positive associations with all chemicals evaluated, indicating that all of these chemicals are causally related to NHL, or more likely, suggesting confounding or other systematic bias. Another important limitation of these studies is that in both crude and multivariable analyses, the definition of unexposed excluded all participants with exposure to any of the chemicals investigated. If cases are more likely to be users of other chemicals than controls, either because one of these chemicals is a cause of NHL or there is another cause related to use of these other chemicals, then the investigators are unintentionally sampling on exposure, leading to selection bias. Information on potential confounders was either not collected or not controlled for in the analyses, which is of particular concern for a study of NHL, where few known risk factors have been identified.

Eriksson *et al*., 2008[6]

Study design. Eriksson *et al.* conducted a population-based case-control study of NHL within 4 of 7 health care regions in Sweden. The study included a total of 910 NHL cases (29 exposed) aged 18-74 years diagnosed between 1999-2002 and 1016 controls

(18 exposed) matched on health care region, age group (in 10-year categories), and sex identified from the national population register. Exposure was assessed by a mailed questionnaire and then supplemented by a telephone interview blinded to case-control status when necessary between 1999-2002. The response rates were 91% in cases and 92% in controls. Additional analyses looked at two groups of glyphosate exposure (dichotomized 10 days based on the median number of exposed days in controls). Multivariable analyses were only conducted for chemicals with a statistically significant odds ratio in univariable analyses or if the odds ratio for a given chemical was at least 1.5 and had minimum of 10 exposed participants. Multivariable analyses were not conducted for analyses that took into account latency or multiple exposure categories.

Results. Statistically significant or suggestive positive associations were identified not only for glyphosate, but also for all of the individual chemicals evaluated. Using unconditional logistic regression controlling for the matching factors, the odds ratio for the association between glyphosate and NHL was 2.02 (95% CI: 1.10-3.71). The odds ratio was attenuated to 1.5 (95% CI: 0.77-2.94) after adjustment for other chemicals, consistent with the presence of confounding by these variables. In an analysis assuming a 10-year latency period but not controlling for other chemicals, the odds ratio for glyphosate was 2.3 (95% CI: 1.2-4.4). The associations of other chemicals with NHL also existed when a 10-year latency period was assumed (2,4,5-T and/or 2,4-D: OR 1.72 (95% CI: 0.98-3.19); MCPA: OR 2.81 (95% CI: 1.27-6.22)). In the analysis of subgroups based on median exposures in the controls (10 days), also uncontrolled for other chemicals, $\leq$10 days of exposure was associated with an odds ratio of 1.69 (95% CI: 0.70-4.07) and >10 days of exposure was associated with an odds ratio of 2.36 (95% CI: 1.04-5.37). In analyses of specific NHL subtypes, the strongest associations were observed for lymphocytic lymphoma (OR: 3.35; 95% CI: 1.4-7.9) and unspecified NHL (OR: 5.63; 95% CI: 1.4-22).

Internal validity. As described previously, the univariable odds ratio for every single chemical evaluated is above one and several are statistically significant. These findings can be explained by confounding or by another systematic bias. The methods for exposure assessment in cases and controls with respect to questionnaire and telephone interview procedures are somewhat vague, making it difficult to determine what

strategies were undertaken to minimize recall bias. The control for other variables and pesticides attenuates the odds ratio from 2.02 (95% CI: 1.10-3.71) to 1.51 (95% CI: 0.77-2.94), suggesting the presence of confounding. Notably, latency and dose-response analyses did not control for confounding. However, in the latency analysis, no cases exposed to MCPA, 2,4,5-T, or 2,4-D were identified in the latency period of 1-10 years because these products had been removed from the market. Therefore, confounding by these other chemicals could not affect the odds ratio for glyphosate in this latency period, which was consistent with no association (1.1; 95% CI: 0.24-5.08). In the >10 year latency period, however, these other chemicals were significantly or strongly suggestive of a positive association with NHL. The association between 2,4,5-T and/or 2,4-D and NHL for >10 years latency was 1.72 (95% CI: 0.98-3.19) and for MCPA was 2.81 (95% CI: 1.27-6.22). In short, if use of glyphosate and those other chemicals is associated (i.e. participants using glyphosate also use those other chemicals), confounding would spuriously inflate the odds ratio for glyphosate in the >10 year latency period (OR 2.26; 95% CI: 1.16-4.40).

Selection bias is an important potential threat to the validity of this study given exclusions in the analyzed controls. In both univariable and multivariable analyses, the same definition of "unexposed" was used as reported in Hardell and Eriksson[3] and Hardell *et al.*[4]. Controls were drawn from the Swedish population registry in an attempt to ensure that the controls reflected the exposure distribution of the source population. However, at the analysis stage the unexposed group was required to have no exposure to *any* of the chemicals evaluated, despite the use of multiple chemicals being a common occurrence. It may be helpful to recall the ultimate purpose of the unexposed group. To evaluate causality of the exposure, we want the unexposed group to reflect the experience of the exposed with respect to everything except the exposure of interest. If we could put the exposed group in a time machine and send them back in time to avoid exposure but otherwise do everything the same, we would <u>not</u> end up with the experience of the controls in the Eriksson *et al.* paper, a group that never used any other chemicals. The odds ratio from these analyses should be interpreted as the comparison of glyphosate and other chemical exposure to no other chemical exposure on the odds of NHL, rather than the effect of glyphosate exposure to no glyphosate exposure on the odds of NHL. In other

words, it is not possible from this comparison to tease out the association specific to glyphosate. If we assume that there are other chemicals that are associated with NHL risk and therefore a larger proportion of individuals unexposed to glyphosate but exposed to other chemicals in the cases than in the controls, removing from the analysis those unexposed to glyphosate but exposed to other chemicals will reduce the proportion of unexposed cases more than the proportion of unexposed controls. This selection bias would result in an odds ratio that was biased upward.

Strengths of this study include the attempt to look at individual NHL subtypes, which could be etiologically distinct, and the attempt to capture the latency/induction period and dose response. While analyses based on a 10-year latency period suggest a stronger association than analyses based on all cases (OR: 2.26; 95% CI: 1.16-4.40), it is important to keep in mind that these analyses were not adjusted for potential confounders and other pesticides, especially when multivariable analyses in the entire study population are consistent with the presence of confounding. The use of a 10-year cut-point is appropriate for an exploratory analysis where more detailed information on the required induction/latency period is not available. However, the corresponding results should be interpreted accordingly as hypothesis generating rather than over-interpreted causally.

As with the latency analysis, the threshold for dichotomization for dose response of 10 days was selected somewhat arbitrarily, in this case based on the median number of exposed days in controls. Thus, the high category for dose response reflects a low level of total exposure and limited range of exposure days when compared to the cohort analysis in the Agricultural Health Study discussed previously. This analysis also did not incorporate intensity of exposure or use of protective equipment. The Acquavella *et al.*[17] biomarker study indicates that a crude assessment of self-reported exposure may not be biologically relevant.

Precision. While including 29 exposed cases makes this study substantially larger than the other Swedish case-control studies, potentially large enough to be considered as evidence in making determinations about causality, the precision of the odds ratio estimates is meaningful only if we believe the study has achieved internal validity. The aforementioned limitations raise serious concerns about confounding and systematic bias.

Furthermore, the number of cases becomes very sparse within NHL subtype categories. The obtained results could serve as the basis for a prospective study that addresses the major limitations, but cannot be taken as evidence of a causal association.

Hardell and Eriksson, 1999[3]

Of 404 male NHL cases in this study, only 4 were exposed to glyphosate. Among the 2:1 matched controls, only 3 were exposed to glyphosate from Northern and Central Sweden. Therefore, this study is based on too little information to provide evidence of causality. Like the Eriksson *et al.* study, the authors identified associations with all chemicals evaluated, suggesting confounding or other systematic bias.

Hardell *et al.*, 2002[4]

The Hardell *et al.* 2002 study represents an attempt to address the limited numbers of NHL cases in the Hardell and Eriksson 1999 study by conducting a pooled analysis of two population-based case-control studies in Sweden. A pooled analysis reanalyzes the primary data collected from prior studies, in this case data from a study of NHL previously reported in Hardell and Eriksson 1999, and another study of hairy cell leukemia. However, the pooled study included just 8 exposed cases among a total of 404 NHL cases and 121 hairy cell leukemia cases. Given that the analysis was based on a total of just 8 exposed cases, this study is not informative for making determinations about causality. Like the other Swedish studies, positive associations were identified for all chemicals evaluated, pointing to confounding or systematic bias.

2. North American Case-Control Studies

The timing of introduction of glyphosate into the market is an important consideration for the interpretation of the U.S.-based case-control studies. Cases included in the American studies were diagnosed between 1979-1986. Glyphosate was not approved for use in agricultural settings until December 1975 [32]. Therefore, the *maximum* induction/latency period between exposure and NHL diagnosis in those studies is 10-11 years, assuming that a participant used glyphosate as soon as it was available and that less than one year of exposure is required to produce a tumor. While induction periods are

specific to particular exposures and outcomes, studies of cancer would ideally aim to allow for a *median* induction/latency period of at least a decade.

Cantor *et al.*, 1992[8]

Study design. The study conducted by Cantor *et al.* was a population-based case-control study of white men in Iowa and Minnesota. Cases included incident NHL cases 30 years and older identified from the Iowa State Health Registry from March 1981-October 1983, and a "special surveillance" of Minnesota hospital and pathology records to ascertain cases diagnosed between October 1980-September 1982. Cancer cases residing in the major metropolitan areas in Minnesota were excluded. Controls included 1245 men matched to cases on vital status, age (within 5-year category) and state of residence. Controls for living cases were identified from random digit dialing and Medicare records. Controls for deceased cases were identified by death certificates. The response rate was 89% for NHL cases and ranged from 77-79% for controls depending on control source, leaving 622 cases (26 exposed to glyphosate) and 1245 controls (49 exposed to glyphosate) for analysis. Exposure was classified as either ever having been exposed or never having handled each chemical of interest. While the analysis of some individual chemicals did control for other pesticides, multivariable adjustment was restricted to chemicals available before 1965, which does not include glyphosate.

Results. Using logistic regression adjusted for the matching factors, smoking status, family history of lymphopoietic cancer, high-risk occupation and high-risk exposures, there was no statistically significant association between glyphosate and NHL (OR: 1.1; 95% CI: 0.7-1.9).

Internal validity. For studies of cancer where latencies have been estimated to be in the range of a decade or more, a median of 10 years between exposure and diagnosis would be appropriate in order to ensure that exposure preceded the outcome. The Cantor *et al.* study evaluated NHL cases diagnosed between October 1980 - October 1983. Given that glyphosate was not available prior to 1975, cases of NHL diagnosed early in follow up may not have been exposed to glyphosate prior to disease development. Confounding is also a concern. However, for confounding by use of another pesticide to conceal an existing positive association between glyphosate and NHL, one of two

scenarios would be required: 1) users of glyphosate would have to be less likely to use other pesticides and those pesticides would have to be associated with higher NHL incidence; however, we know from De Roos *et al.* 2005 that users of glyphosate are very likely to use other chemicals; or 2) users of glyphosate would have to be more likely to use other pesticides and those pesticides would have to be associated with lower NHL incidence (i.e., protective association).

Precision. This study included a large number of cases and produced reasonably narrow confidence intervals around the null value. However, the potential lack of temporality of exposure raises concerns about the validity of the point estimate.

De Roos et al., 2003[9]

Study design. De Roos *et al.* conducted a pooled analysis of three case-control studies of pesticides and NHL from Midwestern states. Male cases aged 21 years and older from Nebraska were identified from the Nebraska Lymphoma Study Group between July 1983-June 1986. As in the study by Cantor *et al.* [8], male cases aged 30 years and older were ascertained from the Iowa State Health Register from 1981-1983 and a surveillance system of the Minnesota hospitals and pathology labs from 1980-1982. A random sample of white male cases diagnosed between 1979-1981 aged 21 years and older was selected from the Kansas State Cancer Registry. For comparability between studies, all cases who worked on a farm prior to age 18 but not after age 18 were excluded. Controls were selected from the same geographical area and frequency matched to cases based on race, sex, age, and vital status using random digit dialing and Medicare records for living cases and death records for deceased cases. Unconditional logistic regression analyses were adjusted for the matching factors, but were not further adjusted for smoking, family history or education, despite the availability of this data, because these variables were deemed not to be important confounders. The authors also utilized a less common analytic strategy, hierarchical logistic regression, in order to evaluate the impact of the use of multiple pesticides.

Results. The association between glyphosate and NHL from logistic regression controlling for only the study matching factors was 2.1 (95% CI: 1.1-4.0)[vi]. Using hierarchical logistic regression to control for use of other pesticides, the association was attenuated to 1.6 (95% CI: 0.9-2.8).

Internal validity. As in the Cantor *et al.* study[8] that contributed data to the De Roos *et al.* study, the maximum window between exposure and outcome, which is restricted by glyphosate's availability on the market and the restriction to cases diagnosed between 1979-1986, is likely too short to allow for latency between a causal agent and cancer development. The possibility that the logistic regression odds ratios are confounded is supported by the attenuation of the odds ratio estimate when hierarchical logistic regression is used. Notably, hierarchical logistic regression relies on a number of assumptions that may not be appropriate for the adequate control of confounding by other pesticides. Lastly, there are a high number of proxy respondents raising concerns about recall bias. Subsequent analyses in the NAPP[11] demonstrated that inclusion of proxy respondents inflated the odds ratio estimates.

Precision. This study included a large number of cases and produced reasonably narrow confidence intervals around the null value. However, the potential lack of temporality of exposure and potential confounding raises concerns about the validity of the point estimate.

McDuffie *et al.*, 2001[7] and Hohenadel *et al.*, 2011[33]

Study design. The study conducted by McDuffie *et al.* is a population-based case-control study of male residents of six Canadian provinces aged 19 and older. NHL cases were diagnosed between 1991-1994 and identified through the provincial cancer registries with the exception of Quebec, where cases were hospital-based. Controls were selected randomly from the provincial health insurance records, telephone listings, or voters' lists. Questionnaires that assessed demographics, medical history, occupational history, family history of cancer, occupational exposure to selected substances, smoking

[vi] Although the title of Table 3 in De Roos 2003 suggests that the standard logistic regression controls for other pesticides, the methods section states that the standard logistic regression models only controlled for study matching factors.

history, and use of protective equipment were mailed to participants. Response rates were 67% for NHL cases and 48% for controls. A telephone interview was used to obtain more detailed information about exposure to specific pesticides in 119 NHL cases and 301 control subjects who had indicated at least 10 hours per year of exposure. Another 60 NHL cases and 155 controls randomly sampled from among those who reported less than 10 hours of exposure per year were also interviewed by telephone. An analysis to evaluate dose response used two glyphosate exposure categories dichotomized at <2 and ≥2 days of exposure. An analysis within the same study population that aimed to more specifically investigate the effect of combinations of agricultural chemicals or agricultural chemicals by themselves was published by Hohenadel *et al.*

Results. In the univariable analysis that included 51 glyphosate-exposed cases and 133 exposed controls, the odds ratio was 1.26 (95% CI: 0.87-1.80). In analyses that adjusted for variables found to be independently associated with the outcome (but not other chemicals), the odds ratio for glyphosate was 1.20 (95% CI: 0.83-1.74). No analyses were undertaken to control for use of other pesticides. However, many other chemicals were also either statistically significantly associated (Mecoprop and Dicamba) or showed suggestions of associations with NHL (2,4-D) in univariable analyses. In analyses of glyphosate exposure in two categories, the odds ratios compared to no exposure were 1.00 (0.63-1.57) for <2 days and 2.12 (2.30-3.73) for ≥2 days of exposure. In the Hohenadel follow-up study of joint exposure to two chemicals, the odds ratios were 0.92 (95% CI: 0.54-1.55) for glyphosate, 1.95 (95% CI: 1.29-2.93) for malathion, and 2.10 (95% CI: 1.31-3.37) for the combination of malathion and glyphosate.

Internal validity. The low response rates in this study, particularly among controls, increase the likelihood that controls do not reflect the underlying source population in terms of exposure distribution. Therefore, selection bias is a concern in this study. Unlike many of the other studies, however, the authors collected information on a variety of potential confounders and provided a table that illustrated how these variables were related to case-control status. Appropriately, the authors controlled for these variables in the analysis, but only minimal evidence of confounding by these variables was suggested. However, the authors did not simultaneously control for the use of chemicals other than glyphosate, raising concerns about residual confounding, especially given that other

chemicals were also related to NHL risk. All of the chemicals evaluated were at least suggestive of a positive association, pointing to confounding or some other type of systematic bias. In fact, in the Hohenadel *et al.* follow-up study where joint chemical exposures were considered, an elevated odds ratio for glyphosate was completely dependent on exposure to malathion. These findings mirror the stratified analysis example for malaria (see p. 11-12) where the apparent association with male gender was no longer present after stratification by indoor vs. outdoor occupation. If we do not separately consider the association of glyphosate within levels of malathion (and perhaps other chemicals) we could observe a spurious association with glyphosate.

Dose-response analyses were conducted in the McDuffie *et al.* study, but were not particularly informative because they included very low levels of exposure (2 days per year) in the highest category and did not take into account duration or intensity of exposure. The AHS, by contrast included up to 20 days of cumulative exposure in the lowest category, up to 2,678 days of exposure in the highest category, and also utilized an intensity-weighted measure of exposure[1]. Moreover, the McDuffie *et al.* study only asked about specific pesticide use when participants reported at least 10 hours per year of any pesticide exposure. These participants were then telephoned to obtain more specific details on use. If cases were more likely than controls to report 10 hours of exposure to any pesticide initially, the telephone call may have prompted these cases to report even higher levels of certain pesticide exposures in the telephone interview, leading to recall bias that inflated the odds ratio. As discussed later, the NAPP results are not consistent with a dose-response relationship according to cumulative use or duration of use, further suggesting that the finding of a dose-response relationship in McDuffie *et al.* is the result of bias or chance.

Precision. The study was relatively large in terms of numbers of exposed cases and controls, leading to confidence limits that were narrower than in many of the other case-control studies and very modest and not statistically significant associations for glyphosate. The discussion of the results is appropriately balanced and suggests that the findings should be interpreted as exploratory.

Lee *et al.*, 2004[34]

Study Design. This is a case-control study using the source study population described in Cantor *et al.* However, this study also included cases diagnosed in Nebraska from 1980-1986. The purpose of this study was to determine if asthma and agricultural chemicals acted synergistically on NHL risk. Other than the extended follow up for case diagnosis, which still involves a relatively short maximum latency period, the study design is identical to the description for Cantor *et al*.[8]

Results. The odds ratio for glyphosate and NHL was 1.4 (95% CI: 0.98-2.1) in non-asthmatics and 1.2 (95% CI: 0.4-3.3) in asthmatics. There was no evidence to suggest that the association between glyphosate and NHL differed by asthma history. These odds ratios were not adjusted for use of other chemicals. However, several other chemicals were either statistically significantly (diazinon, malathion, fonofos) associated or suggestive of a positive association in either the asthmatic or non-asthmatic groups.

Internal validity. As in the Cantor *et al*. study[8] that contributed data to this study, the maximum window between exposure and outcome, which is restricted by glyphosate's availability on the market and the restriction to cases diagnosed between 1980-1986, is likely too short to allow for latency between a causal agent and cancer development. A major concern is confounding, especially by other chemicals. There are a high number of proxy respondents raising concerns about recall bias. Subsequent analyses in the NAPP[11] demonstrated that inclusion of proxy respondents inflated the odds ratio estimates.

Precision. While the confidence intervals are reasonably narrow in the group of non-asthmatics, the analysis among the group of asthmatics is too small to be informative and produced extremely wide confidence intervals.

NAPP unpublished abstracts[10-13]

Study design. The NAPP is a pooled analysis of the aforementioned North American case-control studies (De Roos *et al.* 2003; McDuffie *et al.* 2001; and Cantor *et al.* 1992). Therefore, all issues related to study design carry forward to the NAPP study. A total of 1690 NHL cases (113 ever exposed to glyphosate) and 5131 controls are included in the analysis. The increased number of cases allowed for analyses by NHL subtype and 3 separate analyses of dose response (years of exposure, days per year handled, and cumulative number of lifetime days of exposure).

Results. Results are available from oral presentations using PowerPoint slides and a draft manuscript, and vary somewhat according to the date of the presentation. Sometimes different results are obtained because of the decision to control or not to control for other pesticides in the multivariable models, but in other situations the sources of discrepancies are unclear. The August 31, 2015 presentation[10] addresses a concern about the potential impact of the use of proxy respondents on the quality of exposure information in the individual case-control studies. The ORs for glyphosate and NHL in the NAPP are stratified according to whether results are based on proxies and self-respondents or just self-respondents. With the exception of a single dose-response analysis according to frequency of use, all odds ratios based on self-respondents are attenuated compared to odds ratios that incorporate data from proxies (odds ratio decreased from 1.13 to 0.95 for ever use). This presentation also includes results that control for three chemicals, 2,4-D, dicamba and malathion. The analysis that does not control for these chemicals identifies an odds ratio for ever use of glyphosate of 1.43 (95% CI: 1.11-1.83). In analyses adjusted for those other chemicals, the odds ratio is attenuated to 1.13 (95% CI: 0.84-1.51). No subtype of NHL was statistically significantly associated with glyphosate after adjustment for other chemicals. The results from three analyses to address dose-response are inconsistent. Compared to no exposure, there is no association between years of use (>0-≤3.5: OR 1.28 (95% CI: 0.88-1.84); >3.5: OR 0.94 (95% CI: 0.62-1.42)) or lifetime number of days of use (>0-≤7: OR 0.87 (95% CI: 0.52-1.45); >7: OR 1.08 (95% CI: 0.66-1.77)) with NHL risk after controlling for other chemicals. However, odds ratios for the number of days used per year compared to no exposure were 0.74 (95% CI: 0.46-1.19) for >0 and ≤2 days, and 1.73 (95% CI: 1.02-2.94) for > 2 days.

Internal validity. The potential issues of recall bias, selection bias, and the short latency period described above for each individual study remain potential threats to internal validity in the pooled analysis. However, the NAPP analysis addresses some of the other concerns raised for the individual North American case-control studies. First, the use of proxy respondents in the individual case-control studies appear to bias the odds ratios upward. Second, there is evidence of confounding by use of three chemicals included in some multivariable models, suggesting that previous analyses unadjusted for

these chemicals likely found spuriously inflated odds ratios. In addition, it is presumed that controlling for these chemicals was done quite crudely as ever vs. never use, leaving open the possibility for residual confounding by these variables, as well as residual confounding by other chemicals that were not measured finely enough to be associated with outcome. Analyses of dose response are inconsistent across measures reflecting greater use. Given the large number of secondary analyses performed, this raises concern about false-positive findings. Similarly, the NHL subtype analyses do not point to a specific subtype or subset of NHLs for which risk is elevated.

Precision. The number of exposed cases in analyses of ever vs. never use of glyphosate adjusted for other chemicals produces reasonably narrow confidence intervals (n=113; 95% CI: 0.84-1.51). However, the potential threats to internal validity, including recall bias, unmeasured/residual confounding, and the brief latency period in some individual studies render the point estimate for this study questionable.

3. Other Case-Control Studies

Orsi *et al*, 2009[35]

Study design. Orsi *et al.* conducted a hospital-based case-control study in France that included 491 male and female cases diagnosed at 6 hospitals between 2000-2004. Controls included 456 inpatients primarily from the orthopedic or rheumatology departments at the same institution, and were matched to cases on hospital, age (within 3 years) and sex. For analyses of NHL, 244 cases were included. However, only 12 cases and 24 controls reported exposure to glyphosate.

Results. No association was found between glyphosate and NHL (OR:1.0; 95% CI: 0.5-2.2) or glyphosate and all lymphoid neoplasms combined (OR: 1.2; 95% CI: 0.6-2.1).

Internal validity. In hospital-based case-control studies, it is often difficult to define the underlying source population from which cases are drawn, and consequently, it is difficult to determine the appropriate source of controls. If the controls do not reflect the exposure distribution from the source population that gave rise to the cases, selection bias can occur. Without more information on the referral patterns for cancer cases or controls with orthopedic and rheumatologic diagnoses at the institutions included in this study, it is difficult to evaluate how likely selection bias is to occur or the severity of the impact

on the study results. A further limitation of the study is that the investigators could not control for use of other pesticides, creating the possibility for confounding.

Precision. The analysis of glyphosate and NHL was based on only 12 exposed cases, leading to wide confidence limits around the null value.

Cocco *et al.*, 2013[5]

Cocco *et al.* conducted a case-control study of lymphoma in six European countries. Like the studies by Hardell[4] and Hardell and Eriksson[3], this study was not further considered in my review of the evidence on glyphosate because only 4 B-cell lymphoma cases and 2 controls had ever used glyphosate.

D. Evidence synthesis

The results of a single epidemiologic study can rarely, if ever, be used to determine a causal relationship between an exposure and disease. Instead, each observational study must be carefully analyzed according to study quality and internal validity. Only the studies with reasonable internal validity should be synthesized and weighted based on study quality and precision. For some exposures that we now accept to be causally associated with the development of particular cancers – such as smoking and lung cancer, or human papillomavirus and cervical cancer – synthesis is relatively straightforward because studies consistently found very strong, positive associations with the outcome of interest. While a randomized controlled trial of these exposures could not ethically be conducted, the epidemiologic and laboratory data provided overwhelming support for causality.

Analyses of the internal validity of individual studies. The AHS study represents a prospective evaluation of glyphosate and NHL, in which 75% of participants had used glyphosate. This study design of the AHS guards against recall bias and, especially when considering the unpublished update to the study with follow up through 2008, provides decades of potential exposure between glyphosate and NHL development. The collection of information on medical history, lifestyle factors and 50 agricultural chemicals was available to control for confounding. There were no proxy respondents included, which likely improves the quality of information collected. The study utilized linkage with state

and national registries to capture disease outcomes and minimize loss to follow up. A major strength of the study was inclusion of a much larger range of exposures that could be used to more meaningfully evaluate a potential dose-response relationship. It also represents the largest and most powerful study. Therefore, the AHS study should be much more influential in epidemiologic evidence synthesis.

Too few cases exposed to glyphosate are included in the case-control studies by Hardell and Eriksson[3], and Hardell *et al.*[4], and Cocco[5] to make conclusions about causality. Case-control studies reported by Cantor *et al.*[8],Lee *et al.*, and De Roos *et al.*[9] were conducted too soon after the introduction of glyphosate into the market, raising serious concerns about temporality. The Eriksson *et al.* study[6] includes a reasonable number of cases and provides a reasonable induction time between exposure and disease; however, the definition of the unexposed makes this study susceptible to selection bias. Moreover, there is evidence of confounding by other chemicals, but latency analyses and dose-response analyses (based on as little as 10 days of exposure in the highest category) do not adjust for these other chemicals. All chemicals evaluated were associated with NHL, which as the expert report by Dr. Ritz states, is strongly suggestive of recall bias or another form of systematic bias. The same phenomenon occurs in the study by McDuffie *et al.*[7] Two of the case-control studies included dose-response analyses, but these were based on very low levels of exposure even in the highest category, did not incorporate exposure intensity, and did not control for other pesticides.

The NAPP results shed light on the impact of many of the potential problems of the North American case-control studies on the reported associations. For instance, proxy respondents were frequently utilized, raising concerns about the quality of exposure information. An analysis in the NAPP stratified by proxy vs. self-respondents indicates that utilization of proxies made associations appear stronger. Confounding resulting from lack of control for other pesticides was another major concern in the individual North American case-control studies. The NAPP analysis demonstrates that after controlling for three other pesticides, no association is apparent between glyphosate and NHL. Finally, dose-response analyses in the North American case-control studies were based on low levels of exposure for lifetime of use and days per year of use. The NAPP demonstrates that there is no association between years of use of glyphosate or cumulative lifetime

days of use of glyphosate and NHL after adjustment for other chemicals. There was a borderline statistically significant association for the highest category of days per year of exposure after adjustment for 3 other chemicals, but it is important to note that only the studies in Canada and Nebraska collected this information, with almost all cases coming from the Canadian McDuffie *et al.* study with the limitations previously mentioned.

Synthesis. Meta-analyses represent one approach for formally synthesizing evidence from epidemiologic studies, but are inappropriate at this stage for studies of glyphosate and NHL. Meta-analyses do not always adequately account for study quality. As a result, the most influential studies are simply the largest, despite the fact that a large study is no less likely to suffer from systematic bias and confounding than a small study; moreover, spurious findings are more likely to be statistically significant. As a result, there must be confidence in the individual studies included in a meta-analysis to be free from systematic bias before combining results is considered. That condition is not met for the majority of studies of glyphosate and NHL after controlling for potential confounders. In addition, the follow up of the AHS study through 2008 and the more recent pooling of the North American case-control studies in the NAPP are not currently included in any meta-analysis because they were not available because they had not been published. Inclusion of those results would attenuate the summary meta-analysis effect estimate and render it no longer statistically significant[14].

The Bradford-Hill Criteria are commonly used to further synthesize existing study results in order to evaluate whether an exposure/disease relationship is likely causal. However, I would only employ these criteria for a body of epidemiologic evidence if I was reasonably confident that the studies being considered were free from confounding or systematic bias, and had enough precision to rule out chance findings. With the case-control studies of glyphosate and NHL, those conditions are not met. The plaintiff experts Dr. Neugut and Dr. Ritz both utilize the Bradford-Hill criteria to synthesize the existing scientific evidence evaluating the causal relation between glyphosate and NHL, but they include in the synthesis studies in which they had identified a number of important limitations that may have limited internal validity or led to effect estimates that lacked precision. In addition, the interpretations of how existing studies align with the Bradford-Hill criteria are often generous.

Only one of the Bradford-Hill criteria, *temporality*, is actually required for causality, and therefore should be considered the most important. Retrospective case-control studies cannot be used to reliably evaluate temporality. While the investigators sought information about exposure prior to disease development, the fact that cases were already diagnosed with cancer prior to the questionnaire makes these studies insufficient for determining temporal associations. A prospective study, such as the AHS, is required for establishing temporality. Another Bradford-Hill criterion, *strength* of the association, is important in part because a small relative risk is much more likely to be completely explained away by confounding or other bias than a very large relative risk. For instance, relative risks for HPV and cervical cancer are in the range of 50 to several hundred [36]; even if the results of studies were somewhat confounded away from the null, it could not account for most of the association in the HPV studies. Point estimates for associations below 2.0 would be considered modest – not strong – and would not satisfy the strength criterion. *Dose-response* analyses in the two case-control studies were based on very low levels of exposure and were not controlled for other chemicals that could potentially confound the association. The AHS cohort study, on the other hand, found no evidence of a dose response despite much higher levels of exposure in the highest categories. Therefore, there is no strong evidence supporting a dose-response relationship. *Consistency* across studies is another Bradford-Hill criterion. While several case-control studies did find point estimates for the association between glyphosate and NHL that were above one, the same was true for nearly all of the other chemicals evaluated in most of these studies, indicating systematic bias or confounding. Finally, *specificity* is not particularly useful for determining causality in cancer, because we now know that there are exposures associated with many cancer types (HPV and cervical, anal, penile, and oropharyngeal cancer; smoking and lung, esophagus, kidney, bladder, and acute myeloid leukemia).

The overwhelming majority of epidemiologic studies evaluating glyphosate-based herbicides with respect to NHL are retrospective case-control studies. These studies were either based on very few exposed cases, conducted too soon after the introduction of glyphosate into the market to determine that glyphosate exposure preceded NHL development, or likely influenced by recall bias, selection bias, and confounding. Few

studies were able to control for use of other pesticides, a strong potential confounder, and the confidence intervals for the association of glyphosate and NHL in studies that did control for other chemicals were wide and always included the null value of 1. In fact, several studies identified positive associations between nearly every chemical evaluated and NHL. Therefore, the case-control studies do not offer reliable evidence with which to make any determinations about causality. The AHS, which represents the only prospective study of glyphosate exposure and NHL, and the only study designed specifically to evaluate this research question, found no evidence to support an overall association between glyphosate and NHL, and no evidence to support a dose-response relationship.

E. Response to Plaintiff's experts' reports

In general, I agree with the criticisms of the case-control studies of glyphosate and NHL raised by Drs. Neugut and Ritz. The experts identified small study size and a limited number of exposed cases, issues with a short latency period between glyphosate availability and recruitment of cases, and selection bias as barriers to drawing inferences from these studies. However, in my view, identifying these limitations should result in little weight being given to the case-control studies in the synthesis of evidence for determination of causality. It is also not clear from the report of either Dr. Ritz or Dr. Neugut that there are just five independent epidemiologic studies of glyphosate and NHL that have been analyzed repeatedly; counting every analysis as an independent study of the evidence tends to make the body of epidemiologic evidence on glyphosate and NHL appear much more substantial than in reality.

The forest plot on page 14 of Dr. Ritz's report includes all of the studies without respect to study quality or internal validity. More specifically, the effect estimates chosen represent both adjusted and unadjusted estimates, which could be more strongly influenced by confounding. The table on page 15 of Dr. Ritz's report lists studies according to the number of cases included. However, as mentioned previously, this is not necessarily indicative of the power and precision of the studies because several case-control studies had very limited numbers of exposed cases and controls. In fact, the

Cocco *et al.* study[5] that ranks highest in terms of case numbers is, in fact, one of the least powerful studies because it is based on just 4 exposed cases and 2 exposed controls.

Dr. Ritz's report omits several important limitations of case-control studies of glyphosate and NHL. Dr. Ritz raises the issue of short latency time as a criticism of the Cantor *et al.* study[8], which finds no association between glyphosate and NHL, but this is not raised as an important limitation in the De Roos *et al.*, 2003 study[9], which finds an elevated odds ratio when not adjusting for other chemicals, despite the same interval between exposure and case ascertainment in both studies. With the exception of the low response rates in the McDuffie *et al.* study[7], Dr. Ritz's report did not mention any potential threats to internal validity in the studies by Eriksson *et al.*[6] and McDuffie *et al.*[7] In particular, the fact that both of these studies identified odds ratios above 1 for nearly all of the chemicals evaluated was overlooked. Dr. Ritz emphasizes the results of the NAPP but does not cite the findings that are adjusted for other chemicals, and this adjustment represents a noteworthy methodological improvement over the individual case-control studies.

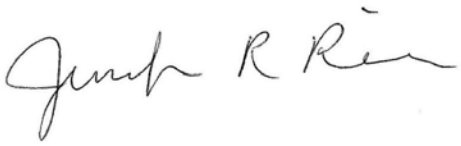
With respect to the AHS cohort study, Dr. Neugut claims that the effect of glyphosate may be underestimated because there is an elevated risk of NHL in participants unexposed to glyphosate. He specifically refers to Table 1 in the De Roos *et al.* 2005 study[1], which shows that 53% of the participants unexposed to glyphosate reported use of 2,4-D, which has been associated with increased risk for NHL. However, Dr. Neugut fails to point out that same table also shows that users of glyphosate are much more likely than non-users of glyphosate to use 2,4-D (as well as other chemicals) and that this trend is positively associated with the level of glyphosate exposure (75.2% in the lowest exposed and 85.1% in the higher exposed). Therefore, confounding by 2,4-D would actually lead to an *overestimate*, not an underestimate, of the rate ratio for glyphosate.

Dr. Neugut also suggests that the latency period between glyphosate exposure and NHL development in the 2005 AHS study is too short. While the median follow-up time between questionnaire administration and NHL diagnosis was 6.7 years, the questionnaire allowed for exposure assessment since the introduction of glyphosate in 1975. There were potentially decades of exposure captured. While the exposure

assessment did require participants to recollect exposure in the distant past, all participants were disease free at the time of the questionnaire, preventing recall bias. Therefore, even in the published AHS manuscript with follow up through 2001, the potential latency period was longer than in any of the case-control studies. The unpublished manuscript with follow up through 2008 should provide even more reassurance that a sufficient latency period was captured and that patients were followed until an age appropriate for NHL diagnosis.

VII. CONCLUSION

My conclusion is that the epidemiologic evidence does not provide a basis sufficient to opine that glyphosate-based herbicides are causally related to NHL.



July 31, 2017

References

1. De Roos AJ, Blair A, Rusiecki JA, et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect* 2005; **113**(1): 49-54.
2. Alavanja MC, Hofmann J, Lynch CF, et al. Lymphoma risk and pesticide use in the Agricultural Health Study. *Unpublished manuscript* 2013.
3. Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 1999; **85**(6): 1353-60.
4. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma* 2002; **43**(5): 1043-9.
5. Cocco P, Satta G, Dubois S, et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. *Occup Environ Med* 2013; **70**(2): 91-8.
6. Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer* 2008; **123**(7): 1657-63.
7. McDuffie HH, Pahwa P, McLaughlin JR, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001; **10**(11): 1155-63.
8. Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992; **52**(9): 2447-55.
9. De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 2003; **60**(9): E11.
10. Pahwa M, Freeman LB, Demers PA, et al. An evaluation of glyphosate use and the risks of NHL major histological subtypes in the North American Pooled Project. International Society for Environmental Epidemiology; 2015 August 31, 2015; Sao Paulo, Brazil; 2015.
11. Occupational Cancer Research Centre. An detailed evaluation of glyphosate use and the risk of non-Hodgkin lymphoma in the North American Pooled Project (NAPP. CSEB Conference; 2015 June 3, 2015; Mississauga, Ontario; 2015.
12. Pahwa M, Beane Freeman LE, Spinelli JJ, et al. A detailed assessment of glyphosate use and the risks of non-Hodgkin lymphoma overall and by major histological sub-types: findings from the North American Pooled Project. IARC @ 50 Conference; 2016 June 10, 2016; Lyon, France; 2016.
13. Pahwa M, Beane Freeman LE, Spinelli JJ, et al. An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP). 2015 (Unpublished draft).
14. Chang ET, Delzell E. Meta-analysis of glyphosate use and risk of non-Hogkin lymphoma: Exponent, 2017.
15. World Health Organization. Health topics: Epidemiology. 2017. http://www.who.int/topics/epidemiology/en/ (accessed May 22, 2017 2017).
16. Szklo M, Nieto FJ. Epidemiology: Beyond the Basics. 3rd edition ed. Burlington, Massachusett: Jones and Bartlett Learning; 2014: 165-7.

17. Acquavella JF, Alexander BH, Mandel JS, et al. Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environ Health Perspect* 2004; **112**(3): 321-6.
18. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004; **15**(5): 615-25.
19. Stark JR, Wiklund F, Gronberg H, et al. Toll-like receptor signaling pathway variants and prostate cancer mortality. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2009; **18**(6): 1859-63.
20. American Cancer Society. About Non-Hodgkin Lymphoma. 2017. https://http://www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html (accessed May 24, 2017.
21. Perry AM, Diebold J, Nathwani BN, et al. Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. *Haematologica* 2016; **101**(10): 1244-50.
22. National Cancer Institute. SEER Cancer Stat Facts: Non-Hodgkin Lymphoma. http://seer.cancer.gov/statfacts/html/nhl.html (accessed May 24, 2017.
23. Melbye M, Ekstrom Smedby K, Trichopoulos D. Chapter 27: Non-Hodgkin Lymphoma. In: Adami HO, Hunter D, Trichopoulos D, eds. Textbook of Cancer Epidemiology. 2 ed. New York, NY: Oxford University Press; 2008: 669-93.
24. Dubrow R, Paulson JO, Indian RW. Farming and malignant lymphoma in Hancock County, Ohio. *Br J Ind Med* 1988; **45**(1): 25-8.
25. Wigle DT, Semenciw RM, Wilkins K, et al. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst* 1990; **82**(7): 575-82.
26. Blair A, Tarone R, Sandler D, et al. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. *Epidemiology* 2002; **13**(1): 94-9.
27. Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* 1993; **4**(1): 55-62.
28. Engel LS, Seixas NS, Keifer MC, Longstreth WT, Jr., Checkoway H. Validity study of self-reported pesticide exposure among orchardists. *J Expo Anal Environ Epidemiol* 2001; **11**(5): 359-68.
29. Hoppin JA, Yucel F, Dosemeci M, Sandler DP. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. *J Expo Anal Environ Epidemiol* 2002; **12**(5): 313-8.
30. Sorahan T. Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) data. *Int J Environ Res Public Health* 2015; **12**(2): 1548-59.
31. Alavanja MC, Hofmann JN, Lynch CF, et al. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. *PLoS One* 2014; **9**(10): e109332.
32. Taylor RJ. EPA Reg. No. 524-308. In: Agency EP, editor. Washington, D.C.; 1975.

33. Hohenadel K, Harris SA, McLaughlin JR, et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. *Int J Environ Res Public Health* 2011; **8**(6): 2320-30.
34. Lee WJ, Cantor KP, Berzofsky JA, Zahm SH, Blair A. Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. *Int J Cancer* 2004; **111**(2): 298-302.
35. Orsi L, Delabre L, Monnereau A, et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occup Environ Med* 2009; **66**(5): 291-8.
36. Bosch FX, de Sanjose S. Chapter 1: Human papillomavirus and cervical cancer--burden and assessment of causality. *J Natl Cancer Inst Monogr* 2003; (31): 3-13.

Exhibit A

Curriculum Vitae

Date Prepared: **April 15, 2017**

Name: **Jennifer R. Rider**

Office Address: **Boston University School of Public Health, 715 Albany Street, Talbot 317E, Boston, MA 02118**

Home Address: [redacted]

Work Phone: [redacted]

Work Email: [redacted]

Place of Birth: [redacted]

Education

1997	BS	Zoology	University of Wisconsin-Madison Madison, Wisconsin
2004	MPH	Public Health	University of Massachusetts-Amherst Amherst, Massachusetts
2008	ScD	Epidemiology	Harvard T.H. Chan School of Public Health Boston, Massachusetts

Postdoctoral Training

05/08-06/09	Research Fellow	Epidemiology	Harvard T.H. Chan School of Public Health
05/08-06/09	Research Fellow	Epidemiology	Channing Laboratory, Brigham and Women's Hospital, Massachusetts

Faculty Academic Appointments

07/09-06/13	Instructor	Channing Division of Network Medicine (formerly Channing Lab), Department of Medicine	Harvard Medical School
09/09-12/09	Adjunct Lecturer	College of Arts and Sciences	Brandeis University Waltham, Massachusetts
09/11-11/13	Instructor	Department of Epidemiology	Harvard T.H. Chan School of Public Health
07/13-9/15	Assistant Professor of Medicine	Channing Division of Network Medicine, Department of Medicine	Harvard Medical School

12/13-9/15	Assistant Professor	Department of Epidemiology	Harvard T.H. Chan School of Public Health
10/15-	Assistant Professor	Department of Epidemiology	Boston University School of Public Health
10/15-	Adjunct Assistant Professor	Department of Epidemiology	Harvard T.H. Chan School of Public Health

Appointments at Hospitals/Affiliated Institutions

2002-2004	Research Coordinator	Department of Hematology, Oncology	University of Massachusetts Medical School Worcester, Massachusetts
2004-2006	Consultant	Department of Hematology, Oncology	University of Massachusetts Medical School
2005-2008	Graduate Research Assistant	Channing Laboratory, Department of Medicine	Brigham and Women's Hospital Boston, Massachusetts
2009 -2015	Associate Epidemiologist	Channing Division of Network Medicine (formerly Channing Lab), Department of Medicine	Brigham and Women's Hospital
2010-2011	Visiting Scientist	Department of Urology	Örebro University Hospital Örebro, Sweden

Major Administrative Leadership Positions

2009	Course Director, Introduction to Epidemiology, Biostatistics and Population Health	Program in Health: Science, Society and Policy, College of Arts and Sciences, Brandeis University
2011-13	Course Director, EPI518: Infections and Cancer	Department of Epidemiology, Harvard T.H. Chan School of Public Health
2014	Course Director, EPI224: Cancer Prevention	Department of Epidemiology, Harvard T.H. Chan School of Public Health
2015	Co-Chair, Epidemiology Department Doctoral Admissions Committee	Department of Epidemiology, Harvard T.H. Chan School of Public Health
2017-	Epidemiology Department Representative, Faculty Senate	Boston University School of Public Health

Committee Service

Local and Regional

2004-2008	Student Advisory Committee 2004-2008	Department of Epidemiology, Harvard T.H. Chan School of Public Health Doctoral Student Member
2012-14	Cancer Epidemiology Admissions Committee	Department of Epidemiology, Harvard T.H. Chan School of Public Health

	2012-14	Member
2012-15	Cancer Epi, Prostate Cancer Program	Dana Farber/Harvard Cancer Center
	2012-	Member
2013-15	Peer Mentoring Program	Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital
2013-15	Cancer Epidemiology Training Grant	Faculty Mentor
2015	MPH-EPI Program Mentoring Committee	Department of Epidemiology, Harvard T.H. Chan School of Public Health
	2015	Member
2015-	MPH Admissions Committee	Boston University School of Pubic Health
	2015-	Member
2015-	Cancer Epidemiology Program	BU-BUMC Cancer Center
	2015-	Member
2016-	Jr Faculty Community Group Organizing Committee	BUSPH
	2016-	Co-Chair

Professional Societies

2008-2011	American Association of Cancer Research	
	2008-2011	Associate Member

Grant Review Activities

2011	Population-Based Research Panel	US Army Prostate Cancer Research Program
	2011	Ad hoc Member
2012-	Prostate Cancer UK Research Awards Panel	Prostate Cancer UK
	2012	Ad hoc Member
2013-15	Detection, Diagnosis, and Prognosis Panel	US Army Prostate Cancer Research Program
	2013-15	Ad hoc Member
2015	PCF Movember-PCF Challenge Award	Prostate Cancer Foundation
	2015	Ad hoc Member
2015-16	PCF Young Investigator Award Review Panel	Prostate Cancer Foundation
	2015-16	Ad hoc Member
2016	PCF Challenge Award Review Panel	Prostate Cancer Foundation
	2016	Ad hoc Member
2016	CTSI Pilot Grant Program	Boston University Clinical and Translational Science Institute (CTSI)
	2016	Ad hoc Member

Editorial Activities

Ad Hoc Reviewer

Health Education Research
Cancer Epidemiology, Biomarkers and Prevention
American Journal of Pathology
Human Immunology
Menopause

Cancer Causes and Control
The Prostate
American Journal of Clinical Nutrition
Clinical Cancer Research
British Medical Journal
Cancer Immunology Immunotherapy
Experimental and Molecular Pathology
Journal of Urology
European Urology
Urologic Oncology
Prostate Cancer and Prostatic Diseases
British Journal of Urology International
Family Medicine and Community Health
BMC Urology
Scandinavian Journal of Urology and Nephrology
Cancer Research
BMC Cancer
Oncotarget
PLOS One

Other Editorial Roles

2009-14	Statistical Reviewer	Menopause
2015-	Associate Editor	Cancer Causes and Control

Honors and Prizes

2005	Travel Award	American Urological Association	Awarded to present abstract at Inflammation in Prostate Diseases Meeting, Linthicum, MD
2006 2008-2009	Scholar-in-Training Award	American Association of Cancer Research	Awarded to present abstract at Frontiers in Cancer Prevention Annual Meeting
2007	Certificate of Distinction in Teaching	Office of the Dean for Undergraduate Education, Harvard College	Teaching undergraduates in QR50: Medical Detectives
2008	Dependent Care Fund Award	Harvard University	
2009-15	NIH Loan Repayment Program Recipient	National Cancer Institute	
2011	Family Care Travel Award	Brigham and Women's Hospital	
2011-13	Teaching Commendation	Committee for Educational Policy, Harvard School of Public Health	Teaching graduate students in Infections and Cancer
2012	First Place Abstract	Prostate Cancer Foundation	American Urological Association Annual Meeting, Atlanta, GA

	Best Poster in Session	American Urological Association	American Urological Association Annual Meeting, Atlanta, GA
	Michael and Lori Milken-PCF Young Investigator Award	Prostate Cancer Foundation	
2013	Family Care Travel Award	Brigham and Women's Hospital	
	The Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine	Harvard Medical School	
	Best Clinical Research Paper of 2013	*European Urology*	

Report of Funded and Unfunded Projects

Funding Information

Past

2007-2010 The infectious pathogenesis of prostate cancer
US Army Medical Research Program Idea Development Award
Graduate Student/Post-doc (PI: Adami)
Growing epidemiologic, genetic, and pathology data point to the role of chronic inflammation in the pathogenesis and progression of prostate cancer. Utilizing the Swedish Watchful Waiting Cohort, a population-based cohort of 1,498 Swedish men diagnosed with localized prostate cancer followed for nearly 30 years, we critically evaluated the initial findings on infections associated with prostate cancer, xenotropic murine-like retrovirus (XMRV), and *Trichomonas vaginalis*.

2008-2010 The patho-epidemiology of proliferative inflammatory atrophy
Dana Farber/Harvard Cancer Center Prostate SPORE Career Development Award
PI
Total direct costs: $80,000
The purpose of this project was to identify predictors and outcomes of chronic and acute inflammation, focal prostatic atrophy, and prostatic intraepithelial neoplasia (PIN) lesions in prostate cancer. Using data from the Physicians' Health Study and Health Professionals Follow-up Study, we evaluated prostatectomy specimens of 1,577 men for the presence and extent of inflammation, atrophy, and PIN.

2010-2011 Intergenerational and perinatal patterns of infectious exposure and the risk of Hodgkin's lymphoma
Örebro County Council Research Committee (Sweden)
Co-Investigator (PI: Montgomery)
We hypothesized that maternal immunological characteristics may influence the offspring's response to infections and thus Hodgkin lymphoma risk. We are conducting a case-control study of Hodgkin lymphoma using Swedish register data to examine if

markers of exposure to microorganisms during the mothers' childhood are association with Hodgkin lymphoma risk among the offspring. We will also examine birth by Caesarean section and other exposures that represent atypical patterns of microorganism exposure in early life in the study participants.

2011-2012 Biomarkers of prostate cancer risk and mortality among men with a benign trans-urethral resection: A nested case control study
Lions Cancerfonden, Örebro University Hospital
PI
Total Direct Costs: 10,000 SEK
We are undertaking a case-control study nested within 2238 men with symptoms of benign prostatic hyperplasia (lower urinary tract symptoms) and treated with trans-urethral resection of the prostate (TURP) at the University Hospital in Örebro between 1978-1998 with no evidence of cancer in the resected tissue. This grant funded the initial study infrastructure. Evaluation of tissue for the presence of tumor, atrophy, and inflammation was recently completed.

2009-2012 TMPRSS2:ERG and SPINK1 in lethal prostate cancer
NIH/NCI P50CA90381
Co-Investigator (PI: Mucci)
We proposed a comprehensive study in the Physicians' Health Study and Health Professionals Follow-up Study among 1,500 men with prostate cancer, of whom 175 developed lethal disease. We hypothesized that there are three mutually exclusive prostate cancer subtypes: *TMPRSS2:ERG* positive, *SPINK1* positive, and Fusion/*SPINK1* negative.

2013-2014 The Role of Vitamin D in Androgen Signaling in Prostate Tumors
The Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine
Harvard Medical School
PI
Total direct costs: $30,000
The overarching goal of this ongoing study is to develop translatable knowledge around the vitamin D pathway to reduce the risk of advanced and lethal prostate cancer. While tantalizing evidence supports the utility of vitamin for disease prevention and curbing disease progression, it is unclear how to best leverage the properties of vitamin D or how to most accurately identify patients who may derive benefit without a thorough understanding of mechanism. To better understand factors underlying vitamin D's benefits with the goal of informing targeted interventions, we focus on vitamin D's role in androgen signaling using pre-diagnostic circulating vitamin D and archival tumor specimens from men with prostate cancer in the Health Professionals Follow-up Study.

2010-2014 Growth factors and lethal prostate cancer signature
NIH/NCI 1R01CA141298-01A1
Project Director (PI: Stampfer)
Using a case-only design in the Physicians' Health Study and Health Professionals Follow-up Study cohorts among incident prostate cancer cases, we will develop a molecular signature for potentially lethal prostate cancer by comparing the RNA expression profiles of tumor tissue from subsequently lethal cases to tumor tissue from men without known

lethal disease. We will also assess circulating biomarkers and tagging germline polymorphisms in the insulin-like growth factor/insulin axis, comparing lethal cases to men without known lethal disease.

2011-2014 A Systems Biology Approach to Link Nuclear Factor Kappa B Activation with Lethal Prostate Cancer
US Army Medical Research Program W81XWH-11-1-0379
Co-Investigator (PI: Sweeney)
To identify patients with lethal prostate cancer, a systems biology approach will be deployed to develop a risk scoring system. The systems biology approach will make use of the epidemiological, clinical, pathological, and biological data that has implicated nuclear factor kappa B activation in the development of lethal prostate cancer.

2012-2014 Shedding light on stromal-epithelial interactions in prostate cancer carcinogenesis and mortality
Dana-Farber/Harvard Cancer Center (DF/HCC) Sponsored Funding
Co-Investigator (PI: Loda)
Total direct costs: $114,000
We hypothesize that the morphologic progression of normal prostate to PIN to invasive cancer is driven in part by molecular alterations in stromal tissue. In addition, the cross-talk between epithelium and stroma contributes to tumor development and dedifferentiation. We posit that the stroma harbors molecular changes associated with lethal prostate cancer, and that these markers interact with tumor alterations to drive lethal disease. By developing robust bioinformatic approaches, we can disentangle the relative stromal and tumor signals within admixed samples and apply these to prostate cancer expression profiling data sets. The proposed study will test and validate critical pathways in the stromal-epithelial environment associated with prostate carcinogenesis, illuminate alterations in pathways in the microenvironment that drive lethal disease, and develop novel bioinformatic tools to characterize stromal-epithelial cross-talk. We propose to integrate genome wide mRNA and miRNA expression data in cohorts from the US, Sweden and Ireland, and to translate results to detect novel chemopreventive and therapeutic strategies.

2012-2014 Inflammation and tissue microenvironment as predictors of prostate cancer risk, mortality, and therapy response among men with an initially benign TURP
A. David Mazzone Career Development Award
Dana Farber Cancer Institute
PI
Total direct costs: $100,000
Our study aims to pre-diagnostically evaluate aspects of the tissue microenvironment that may contribute to aggressive prostate cancer directly, or may harbor molecular changes that occur in response to carcinogenic stimuli. We have designed a case-control study that includes 182 men diagnosed with prostate cancer following the initial benign TURP and 364 men without a prostate cancer diagnosis for a minimum of 10 years after the initial TURP, matched to cases on age and TURP year in categories. Tissue is currently being evaluated for inflammation and atrophy, and the database incorporating clinical information is being compiled.

2013-2015 Chronic Stress and Racial Disparities in Prostate Cancer
A. David Mazzone Research Program Disparities Research Award
Dana-Farber/Harvard Cancer Center
PI
Total direct costs: $100,000
Using the Southern Community Cohort Study (SCCS), a prospective cohort study of >85,000 participants, two-thirds of whom are African American and more than half of whom live in poverty, we will test the hypothesis that chronic stress increases the risk of prostate cancer and is responsible for some measure of the racial disparity in prostate cancer. We are currently relating environmental and interpersonal stressors on risk of prostate cancer.

2013-2016 The antimicrobial and immunomodulatory actions of vitamin D in prostate cancer
Prostate Cancer Foundation Young Investigator Award
Prostate Cancer Foundation
PI
Total direct costs: $225,000
Using 358 men from the Health Professionals Follow-up Study for whom we have archival tissue and pre-diagnostic blood, we have evaluated the relationship between the circulating and prostatic vitamin D environment with respect to patterns of immune response in tumors. Using a novel mediation analysis, we found that the impact of vitamin D on prostate cancer risk appears to be largely independent of inflammation. An analogous analysis investigating the role of inflammation in androgen-related pathways is currently underway. The culmination of our project will involve testing whether gene sets involved in immune response or androgen signaling are overexpressed according to vitamin D status. We will use the Connectivity Map to link gene sets associated with androgen signaling and immune response with genetic profiles of small molecules and natural compounds to identify potential vitamin D-related therapeutic targets for aggressive prostate cancer.

2013-2018 Prostate SPORE Project 1: Tumor and circulating markers as links between obesity and lethal prostate cancer
NIH
Co-Investigator (PI: Kantoff)(Project PI: Mucci)
Total direct costs: $107,259
This project is the population-based science project as part of the DF/HCC SPORE in Prostate Cancer resubmission. The objective is to elucidate the underlying links between obesity and lethal disease among men with incident prostate cancer who were participants in the Health Professionals Follow-Up Study. We are proposing to investigate specific pathways associated with obesity and integrate anthropometric data, molecular features in prostatic tumor and stroma, and circulation biomarkers measured in pre-diagnostic blood samples with cancer outcomes.

2015-2016 Adiposity and prostate health
Collaborative Research Award
David Rockefeller Center for Latin American Studies, Harvard University
PI
Total direct costs: $5,050

This award will support future planning and a pilot study on "baseline" PSA levels in a cohort of male teachers in Mexico. We are specifically interested in the impact of measures of adiposity and metabolic syndrome on PSA as Mexico undergoes a major epidemiologic shift towards a more Western lifestyle.

2016 A Programmatic Intervention to Improve Access to Timely Oncology Care for HIV-Infected Individuals in Botswana
NIH/NCI P30 Cancer Centers Support Grant
Co-Investigator (Co-PIs: Dryden Peterson and Tapela)
This project will evaluate the impact of a multifaceted programmatic intervention to improve timely access to oncology care in Botswana.

Current

2016-17 Gene expression profiles in prostate tumors according to HIV status
BU School of Public Health Early Career Catalyst Award
PI
Total direct costs: $19,254
In light of the growing burden of PCa in HIV-infected men, it is of urgent importance to determine whether the clinical presentation of prostate tumors in HIV-infected men is different from HIV-uninfected men and whether the reduced incidence of PCa in HIV-positive men compared to HIV-negative men is a result of changes in underlying biology, which could potentially be harnessed for PCa prevention or treatment. This pilot study will generate preliminary data for a planned R01 application focused on these clinical and etiological questions. We will utilize tumor specimens from the Urologic Outcomes Database (UODB) at the University of California-San Francisco (UCSF) to address the following specific aims: 1) Evaluate the availability of clinical data and distribution of clinical characteristics of HIV-positive prostate cancer patients in the UODB; 2) Demonstrate the feasibility of using prostate cancer tumor specimens from the UODB for tumor gene expression studies; and 3) Identify differential patters of gene expression in HIV-positive vs. HIV-negative prostate tumors.

Pending

2016-18 A unified observational and interventional study of NCDs in Mexico
NIH/NCI R21
MPI
Total direct costs: $84,192 (SubK)
Our proposal will build on our experience in establishing the female Mexican Teachers' Cohort (MTC), accomplished through a unique partnership with the national public education system, in order to create an observational study of cancer and other NCDs in men. We also aim to evaluate the feasibility of embedding behavioral and lifestyle interventions to facilitate rapid translation of study findings. We will first demonstrate our ability to estimate NCD incidence accompanying rapid changes in lifestyle risk factors including body weight, tobacco use and physical activity. We will also evaluate our capacity to identify novel markers for cancer risk and survival and undertake biospecimen collection (blood, urine, hair, stool and buccal cells). Finally, we will explore the methodological implications of embedding interventions in an observational cohort, as well as assess the feasibility and scalability of such interventions using social media

platforms. Successful completion of our project would contribute substantially to the NCD research capacity in Mexico using cost-effective strategies that leverage existing resources and infrastructure.

Currently unfunded studies

2017-2019 Detection and underlying biology of prostate tumors in HIV-positive versus HIV-negative men
NIH/NCI R21
PI
Total direct costs: $274,921
The life expectancy of HIV-infected individuals has dramatically increased over time as a result of more effective antiretroviral therapies, leading to an increase in the burden of non-AIDS defining cancers, including prostate cancer. HIV-infected men are more likely to be diagnosed at an advanced stage and experience prostate cancer-specific mortality compared to uninfected men, despite an incidence of overall prostate cancer that is lower than the general population. This study will investigate potential factors contributing to prostate cancer disparities in HIV-infected compared to HIV-uninfected men, including differences in PSA detection and underlying tumor biology, to identify whether screening and management strategies should be modified in this population.

2017-2020 Stratification and statin therapy for prostate cancer guided by intratumoral cholesterol synthesis
US Army Medical Research Program
PI
Total direct costs: $1,994,797
Prostate cancer cells need intracellular cholesterol for proliferation, and castration-resistant prostate cancer (CRPC) cells produce androgens from cholesterol. We recently validated that high intratumoral mRNA expression of the second rate-limiting enzyme of cholesterol synthesis, squalene monooxygenase (*SQLE*), measured at cancer diagnosis is associated with a substantially increased risk of lethal cancer. High *SQLE* mRNA expression predicted the failure of androgen-deprivation therapy (ADT) and more tumor angiogenesis. Statin medications inhibit cholesterol synthesis and are associated with less advanced and lethal prostate cancer in epidemiologic studies. The effect of statins is mirrored by SQLE expression. Preclinical data suggest a role of cholesteryl ester accumulation in advanced prostate cancer. We hypothesize that assessing high intratumoral cholesterol synthesis activity can identify prostate cancer patients at risk of tumor progression and those with tumors that will respond favorably to statin therapy. We will translate SQLE mRNA into a clinically relevant protein biomarker and conduct a randomized trial among localized and advanced prostate cancer patients to evaluate the ability of SQLE to predict response to statin therapy on tumor characteristics and tumor progression.

Report of Local and Regional Teaching and Training

Teaching of Students in Courses

2005-08	Analytical Aspects of Clinical Epidemiology/Teaching assistant	Harvard T.H. Chan School of Public Health
	Graduate students	5 2-hr sessions per week for 4 weeks

2006	Medical Detectives/Teaching fellow	Harvard College
	Undergraduates	1 1-hr session per week for 15 weeks
	Elements of Epidemiologic Research/Teaching assistant	Harvard T.H. Chan School of Public Health
	Graduate students	1 2-hr session per week for 8 weeks
2008	Introduction to epidemiology/Guest lecturer	Harvard Extension School
	Graduate students	3 2-hr lectures
2008-09	Principles of Screening/Guest lecturer	Harvard T.H. Chan School of Public Health
	Graduate students	1 2-hr lecture
2009	Introduction to epidemiology/Co-instructor	Harvard Extension School
	Graduate students	5 2-hr lectures
2010	Cancer Epidemiology/Guest lecturer	Harvard T.H. Chan School of Public Health
	Graduate students	1 2-hr lecture
2010-12	Molecular Pathology Boot Camp	Harvard Medical School
	Undergraduate and graduate students	1 2-hr lecture
2011-13	Infections and Cancer/Course director	Harvard T.H. Chan School of Public Health
	Graduate students	2 2-hr sessions per week for 8 weeks
2012-14	Introduction to Clinical Epidemiology/Workshop leader	Harvard School of Public Health
	Graduate students	1 2-hr session
2014	Cancer Prevention/Course director	Harvard T.H. Chan School of Public Health
	Graduate students	2 2-hr sessions per week for 8 weeks
2015	Global Epidemiology	Harvard T.H. Chan School of Public Health
	Graduate students	1 1-hr lecture
2016	Novel Epidemiologic Methods (EP860)	Boston University School of Public Health
	Graduate students	2 2.75-hr lectures
2016	Principles of Cancer Epidemiology (EP735)	Boston University School of Public Health
	Graduate students	1 1.5-hr lecture
2016	Cancer Epidemiology	Harvard T.H. Chan School of Public Health
	Graduate students	1 2-hr lecture
2016	Cancer Prevention	Harvard T.H. Chan School of Public Health
	Graduate students	1 2-hr lecture
2016	Intermediate Epidemiology (EP813)/Course director	Boston University School of Public Health
		14 2-hr lectures; 8 45-min workshops

Laboratory and Other Research Supervisory and Training Responsibilities

2011	Supervision of post-doctoral research fellow	Weekly mentorship for 3 months
2012	Supervision of MPH student for class project	Daily mentorship for 8 weeks
	Supervision of summer research assistant	20 hours/week of mentorship for 8 weeks
2013-	Peer mentoring of 5 post-doctoral fellows and instructors at the Channing Division of Network Medicine	1 hour/month of mentorship for 9 months
2016	Supervision of 2 summer research assistants	20 hours/week of mentorship for 12 weeks

Academic Advisees and Dissertation Review Activities

2016 - MPH Advisor for BUSPH EPI/Biostat Certificate students – Shalini Chalikonda, Ashley

Dauphin, Pei-Rong Lin, Gayatri Pradhan, Jess Rosenberg, Savannah Strohmayer

2016 - Outside Dissertation Reader, Stephen Haddad/BUSPH Epidemiology Doctoral Candidate Gene- and Pathway-Based Genomics of Breast Cancer and Type 2 Diabetes in African American Women

Formally Supervised Trainees

2010 - 13 Sabina Davidson/PhD student in biomedical sciences, Örebro University
Published first manuscript in *Cancer Epidemiology, Biomarkers and Prevention;* published second manuscript in *Modern Pathology;* Received funding from Lions Cancerfonden at Örebro University Hospital

2010 - 13 Maria Svensson/PhD student in biomedical sciences, Örebro University
Received funding from Lions Cancerfonden at Örebro University Hospital; Abstract selected for oral presentation at 2011 U.S. & Canadian Academy of Pathology Annual Meeting

2012 - 14 Julia Udesky/SM2 student in epidemiology, Harvard T.H. Chan School of Public Health (academic advisor/thesis supervisor)

2013 – 14 Nils Hjelm/Medical student, Karolinska Institutet (practicum supervisor)
Konrad Stopsack/MPH (Quantitative Methods) student, Harvard T.H. Chan School of Public Health

2013 - 2014 Erin Onstad/Doctoral student in epidemiology, Harvard T.H. Chan School of Public Health (academic advisor)

2014 - 15 Sarah Markt/Post-doctoral fellow in epidemiology, Harvard T.H. Chan School of Public Health (secondary mentor)

2015-16 Stephanie Johnson-Obaseki/MPH student in clinical effectiveness, Harvard T.H. Chan School of Public Health (practicum supervisor)

2015- Edsel Ing/MPH-EPI student, Harvard T.H. Chan School of Public Health (practicum supervisor)

2015- Nahid Punjani/MPH-EPI student, Harvard T.H. Chan School of Public Health (practicum supervisor)

2016 Theresa Faller/MPH student, BU School of Public Health (practicum supervisor)

2016 Chirag Vargas/MPH student, BU School of Public Health (practicum supervisor)

Local and Regional Invited Presentations

No presentations below were sponsored by outside entities

2006 Interleukin-6, C-reactive protein, and prostate cancer incidence and mortality.
Cancer Epidemiology Training Grant Meeting, Harvard School of Public Health

2007 Gleason score and lethal prostate cancer
John Graunt Meeting, Harvard T.H. Chan School of Public Health

2008 *Trichomonas vaginalis* and prostate cancer incidence and mortality
Molecular Epidemiology Journal Club, Harvard T.H. Chan School of Public Health

2008 Sleep patterns and melatonin in prostate cancer: A prospective study in the Reykjavik Cohort

2008-10	Prostate Cancer Epidemiology/Guest Lecturer in Cancer Epidemiology course Department of Epidemiology Boston University School of Public Health
2009	MTA1 protein expression in prostate cancer Dana Farber/Harvard Cancer Center Prostate Cancer SPORE Meeting
2009	Polymorphisms in adiponectin and adiponectin receptors and prostate cancer survival. Cancer Epidemiology Training Grant Meeting, Harvard T.H. Chan School of Public Health
2009	Sex, bugs, and Toll-like receptors: Infection and inflammation in prostate cancer Department of Epidemiology, Harvard T.H. Chan School of Public Health Introduction to Epidemiology/Visiting Lecturer Colleges of Arts and Sciences, Brandeis University
2012	Inflammation: the state of the (pro)state. Department of Epidemiology seminar, Harvard T.H. Chan School of Public Health
2013	Prostate Cancer Overview Dana Farber/Harvard Cancer Center 'What's Up in Cancer Epidemiology?' Event
2013	Epidemiologic resources and techniques to inform etiology/outcomes of infection-related cancers Center for AIDS Research (CFAR)/DFHCC Cancer-HIV Symposium
2015	Why are there so few risk and prognostic factors for prostate cancer? Department of Epidemiology Seminar/Boston University School of Public Health

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

No presentations below were sponsored by outside entities

National

2008	Obesity and prostate cancer progression in the Physicians' Health Study National Cancer Institute Translational Science Meeting, Washington, D.C.
2008	*Trichomonas vaginalis* infection and prostate cancer incidence and mortality: a prospective study in the Physicians' Health Study/Selected for oral abstract presentation American Association for Cancer Research Frontiers in Cancer Prevention Research Meeting, Washington, D.C.
2009	Does ejaculation frequency impact prostate cancer incidence or mortality? Updated findings from the Health Professionals/Selected as oral abstract presentation Multi-institutional Prostate Cancer SPORE Program Retreat, Baltimore, MD
2010	Post-atrophic hyperplasia lesions and prostate cancer survival/Selected as oral abstract presentation Multi-institutional Prostate Cancer SPORE Program Retreat, Ft. Lauderdale, FL
2011	Adiponectin receptor 2 expression predicts lethal prostate cancer/Selected as oral abstract presentation United States & Canadian Academy of Pathology Annual Meeting, San Antonio, TX
2013	Successful examples of patho-epidemiology collaborations: infections Prostate Cancer Foundation Scientific Retreat, National Harbor, MD
2014	Two decades of follow-up from the SPCG-4 trial: How do the results inform treatment of localized patients today? Prostate SPORE Retreat, Ft. Lauderdale, FL

2015 Ejaculation frequency and risk of prostate cancer: updated results from the Health Professionals Follow-up Study. American Urological Association Annual Meeting, New Orleans, LA
Interpreting screening data, NCI Cancer Prevention Fellowship Program Summer Curriculum, Bethesda, MD
Methodological challenges in identifying risk and prognostic factors for prostate cancer, Fred Hutchinson Cancer Research Center Program in Prostate Cancer Research, Seattle, WA

2016 Identifying the best clinical applications of post-diagnostic biomarkers
First Global Summit on Precision Diagnosis for Prostate Cancer, Boston, MA

International

2006 Case-Control Studies/Guest Lecturer for Epidemiology I
Department of Medicine, Epidemiology, and Biostatistics, Karolinska Institutet, Solna, Sweden

2010-11 Introduction to Epidemiology/Guest Lecturer
National Research School in Psychiatry and Oncology, Karolinska Hospital, Solna, Sweden

2010 Focal prostatic atrophy lesions and lethal prostate cancer/Selected as oral abstract presentation
SiURO (Italian Socieity of Uro-Oncology) Annual Meeting, Rome, Italy

2011 Prostate cancer epidemiology
Clinical Research Center, Örebro University Hospital, Örebro, Sweden

2016 Epidemiology and Cancer Prevention (20-hour course)
Public Health and Epidemiology Upgrading Program (PAPSE), Mexico National Institute of Public Health

2016 Cholesterol metabolism in aggressive prostate cancer
Departmental seminar, Department of Surgery and Cancer, Imperial College London, London, UK

Community Engagement

2014 First Annual Prostate Cancer Teach-In, Harvard T.H. Chan School of Public Health, Boston, MA
Featured Panelist

2015 Prostate Cancer Awareness Day, Massachusetts State House, Boston, MA
Poster Presentation – Modifiable Risk Factors for Prostate Cancer

2016 Prostate Cancer Awareness Day, Massachusetts State House, Boston, MA
Featured Panelist

2016 Prostate Cancer Awareness Event – Honoring Father's Day, Brockton, MA
Featured Speaker

Report of Scholarship

Peer-reviewed publications in print or other media

Research Investigations

1. Costanza ME, Luckmann R, Stoddard A, Avrunin JS, White MJ, **Stark (Rider) JR,** Clemow L, Rosal M. Applying a stage model of behavior change to colon cancer screening. Prev Med 2005;41(3-4):707-19.

2. White MJ, **Stark (Rider) JR.** Implementing a computer-assisted telephone interview (CATI) system to increase colorectal cancer screening: A process evaluation. Patient Educ Couns 2006;61(3):419-28.

3. **Stark (Rider) JR,** Bertone-Johnson E, Costanza ME, Rosal MC, Stoddard AM. Factors Associated with Colorectal Cancer Risk Perception: The Role of Polyps and Family History. Health Educ Res 2006; 21(5):740-749.

4. Costanza ME, Luckmann R, Stoddard AM, White MJ, **Stark (Rider) JR,** Avrunin JS, Rosal MC, Clemow L. Using tailored telephone counseling to accelerate the adoption of colorectal cancer screening in primary care practices. Cancer Detect Prev 2007; 31(3):191-198.

5. LaPelle N, Costanza ME, Luckmann R, Rosal MC, White MJ, **Stark (Rider) JR.** Staging mammography nonadherent women: a qualitative study. J Cancer Educ 2008; 23(2):114-21.

6. Mucci LA, Pawitan Y, Demichelis F, Fall K, **Stark (Rider) JR,** Adami H-O, Andersson S-O, Andrén O, Eisenstein AS, Holmberg L, Huang W, Kantoff PW, Kim R, Perner S, Stampfer MJ, Johansson J-E, Rubin MA. Nine-gene molecular signature in tumors does not predict prostate cancer death. Cancer Epidemiol Biomarkers Prev 2008;17(1):249-51.

7. Mucci LA, Pawitan Y, Demichelis F, Fall K, **Stark (Rider) JR,** Adami H-O, Andersson S-O, Andren O, Holmberg L, Huang W, Kantoff PW, Kim R, Perner S, Stampfer MJ, Johansson J-E, Rubin MA. Testing of a multigene signature of prostate cancer death in the Swedish Watchful Waiting Cohort. Cancer Epidemiol Biomarkers Prev 2008;17(7):1682-8.

8. Fall K, **Stark (Rider) JR,** Mucci LA, Chan J, Stampfer MJ, Kurth T, Febbo PG, Kantoff P, Ma J. No association between a polymorphic variant of the IRS-1 gene and prostate cancer risk. Prostate 2008;68(13):1416-20.

9. **Stark (Rider) JR,** Li H, Kraft P, Kurth T, Giovannucci EL, Stampfer, MJ, Ma J, Mucci LA. Circulating pre-diagnostic interleukin-6 and c-reactive protein, interleukin-6 genotype, and prostate cancer incidence and mortality. Int J Cancer 2009;124(11):2683-9.

10. **Stark (Rider) JR,** Wiklund F, Grönberg H, Schumacher F, Sinnott JA, Stampfer MJ, Mucci LA, Kraft P. Toll-like receptor signaling pathway variants and prostate cancer mortality. Cancer Epidemiol Biomarkers Prev 2009;18(6):1859-63.

11. **Stark (Rider) JR,** Perner S, Stampfer MJ, Sinnott JA, Finn S, Eisenstein A, Ma J, Kurth T, Loda M, Giovannucci EL, Rubin MA, Mucci LA. Gleason score and lethal prostate cancer: Does 3+4 = 4+3?. J Clin Oncol 2009;27(21):3459-64. [Featured as news item in Nat Rev Urol]

12. Mucci LA, **Stark (Rider) JR,** Figg WD, Schumacher F, Li H, Abe M, Hennessey K, Stampfer MJ,

Gaziano JM, Ma J, Kantoff PW. Polymorphism in endostatin, an angiogenesis inhibitor, and prostate cancer risk and survival: a prospective study. Int J Cancer 2009;125(5):1143-1146.

13. **Stark (Rider) JR,** Judson G, Alderete JF, Mundodi V, Kucknoor AS, Giovannucci EL, Platz EA, Sutcliffe S, Fall K, Kurth T, Ma J, Stampfer MJ, Mucci LA. *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: a prospective study in the Physicians' Health Study. J Natl Cancer Inst 2009;101(20):1406-11.[Accompanying editorial]

14. Mucci LA, **Stark (Rider) JR,** Pollak MN, Li H, Kurth T, Stampfer MJ, Ma J. Plasma levels of acid-labile subunit, free insulin-like growth factor-1, and prostate cancer risk: a prospective study. Cancer Epidemiol Biomarkers Prev 2010;19(2):484-91.

15. Fiorentino M, Judson G, Penney K, Flavin R, **Stark (Rider) JR,** Fiore C, Fall K, Martin NE, Ma J, Sinnott JA, Giovannucci E, Stampfer MJ, Sesso H, Kantoff PW, Finn S, Loda M, Mucci LA. Immunohistochemical expression of BRCA1 and lethal prostate cancer. Cancer Res 2010;70(8):3136-9.

16. Meyer MS, Penney KL, **Stark (Rider) JR,** Schumacher F, Sesso H, Loda M, Fiorentino M, Finn S, Flavin R, Kurth T, Price A, Giovannucci EL, Fall K, Stampfer MJ, Ma J, Mucci LA. Genetic variation in *RNASEL* associated with prostate cancer risk and progression. Carcinogenesis 2010;31(9):1597-603.

17. Kirrander P, Kolaric A, Helenius G, Windahl T, Andrén O, **Stark (Rider) JR,** Lillsunde-Larsson G, Elgh F, Karlsson MG. Human papillomavirus prevalence, distribution and correlation to histopathological parameters in a large Swedish cohort of men with penile carcinoma. BJU Int 2011;108(3)355-9.

18. Andersson S-O, Andrén O, Lyth J, **Stark (Rider) JR**, Henriksson M, Adami H-O, Carlsson P, Johansson JE. Managing localized prostate cancer by radical prostatectomy or watchful waiting: cost analysis of a randomized trial (SPCG-4). Scand J Urol Nephrol 2011;45(3):177-183.

19. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, **Stark (Rider) JR,** Busch C, Nordling S, Häggman M, Andersson S-O, Bratell S, Spångberg A, Palmgren J, Steineck G, Adami H-O, Johansson J-E. Radical prostatectomy versus watchful waiting in early prostate cancer – a 15-year follow-up. New England J Med 2011;364(18):1708-17.

20. Penney K, Sinnott JA, Fall K, Pawitan Y, Hoshida Y, Kraft P, **Stark (Rider) JR,** Fiorentino M, Perner S, Finn SP, Calza S, Flavin R, Freedman M, Setlur S, Sesso H, Andersson S-O, Martin N, Kantoff PW, Johansson J-E, Adami H-O, Rubin MA, Loda M, Golub TR, Andrén O, Stampfer MJ, Mucci LA. An mRNA Expression Signature of Gleason Grade Predicts Lethal Prostate Cancer. J Clin Oncol 2011;29(17):2391-6.

21. Wilson KM, Kasperzyk JL, **Rider JR,** Kenfield S, van Dam RM, Stampfer MJ, Giovannucci E, Mucci LA. Coffee Consumption and Prostate Cancer Risk and Progression in the Health Professionals Follow-up Study. J Natl Cancer Inst 2011;103(11):876-84.

22. Davidsson S, Fiorentino M, Andren O, Fang F, Mucci LA, Varenhorst E, Fall K, **Rider JR.** Inflammation, focal atrophic lesions and prostatic intraepithelial neoplasia with respect to risk of

lethal prostate cancer. Cancer Epidemiol Biomarkers Prev 2011;20(10):2280-7.

23. Dhillon PK, Penney KL, Schumacher F**, Rider JR,** Sesso HD, Pollack M, Fiorentino M, Finn S, Loda M, Rifai N, Mucci LA, Giovannucci EL, Stampfer MJ, Ma J. Common polymorphisms in the adiponectin and its receptor genes, adiponectin levels, and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2011;20(12):2618-27.

24. Shui IM, **Stark (Rider) JR,** Penney KL, Schumacher FR, Epstein MM, Pitt MJ, Stampfer MJ, Tamimi RM, Lindstrom, S, Sesso HD, Fall K, Ma J, Kraft P, Giovannucci E, Mucci LA. Genetic variation in the toll-like receptor 4 and prostate cancer incidence and mortality. Prostate 2012;72(2):209-16.

25. Sigurdardottir LG, Valdimarsdottir U, Fall K, **Rider JR,** Lockley SW, Eva SS, Mucci LA. Circadian disruption, sleep loss and prostate cancer risk: a systematic review of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2012;21(7):1002-11.

26. Pettersson A, Graff RE, Bauer SR, Pitt M, Lis RT, Stack EC, Martin NE, Kunz L, Penney KL, Ligon AH, Suppan C, Flavin R, Sesso HD, **Rider JR,** Sweeney C, Stampfer M, Fiorentino M, Kantoff PW, Sanda M, Giovannucci E, Ding EL, Loda M, Mucci LA. The TMPRSS2:ERG rearrangement, ERG expression, and prostate cancer outcomes: a cohort study and meta-analysis. Cancer Epidmiol Biomarkers Prev 2012;21:1497-1509.

27. Epstein MM, Edgren G, **Rider JR,** Mucci LA, Adami H-O. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012;104(17):1335-42.

28. Epstein MM, Andrén O, Kasperzyk JL, Shui IM, Penney KL, Fall K, **Rider JR,** Stampfer MJ, Andersson S-O, Giovannucci E, Mucci LA. Seasonal variation in expression of markers in the vitamin D pathway in prostate tissue. Cancer Causes Control 2012;104(17):1335-42.

29. **Rider JR,** Sandin F, Andrén O, Wiklund P, Hugosson J, Stattin P. Long-term outcomes among non-curatively treated men according to prostate cancer risk category in a nation-wide, population-based study. Eur Urol 2013;63(1):88-96.

30. Chen YC, Huang YL, Platz EA, Alderete JF, Zheng L, **Rider JR,** Kraft P, Giovannucci E, Sutcliffe S. Prospective study of effect modification by *Toll-like receptor 4* variation on the association between *Trichomonas vaginalis* serostatus and prostate cancer. Cancer Causes Control 2013;24(1):175-80.

31. Popiolek M*, **Rider JR*,** Andrén O, Andersson S-O, Holmberg L, Adami H-O, Johansson J-E. Natural history of early, localized prostate cancer: a final report from three decades of follow up. Eur Urol 2013;63(3):428-35. (*Authors contributed equally)

32. Davidsson S, Ohlson A-L, Andersson S-O, Fall K, Meisner A, Fiorentino M, Andrén O, **Rider JR**. CD4 helper T cells, CD8 cytotoxic T cells, and FOXP3+ regulatory T cells with respect to lethal prostate cancer. Modern Pathology 2013;26(3):448-55.

33. Sigurdardottir L, Valdimarsdottir U, Mucci L, Fall K, **Rider JR,** Schernhammer ES, Czisler CA, Launer L, Stampfer M, Guonason V, Lockley SW. Sleep disruption among older men and risk of

prostate cancer. Cancer Epidmiol Biomarkers Prev 2013;22(5):872-9.

34. Schoenfeld JD, Margalit DN, Kasperzyk JL, Shui IM, **Rider JR**, Epstein MM, Meisner A, Kenfield S, Martin NE, Nguyen PL, Kantoff PW, Giovannucci EL, Stampfer MJ, Mucci LA. A single nucleotide polymorphism in inflammatory gene RNASEL predicts outcome after radiation therapy for localized prostate cancer. Clin Cancer Res 2013;19(6):1612-9.

35. Penney KL, Stampfer MJ, Jahn JL, Sinnott JA, Flavin R, **Rider JR,** Finn S, Giovannucci E, Sesso HD, Loda M, Mucci LA, Fiorentino M. Gleason grade progression is uncommon. Cancer Res 2013;73(16):5163-68.

36. Bill-Axelson A, Garmo H, Holmberg L, Johansson J-E, Adami H-O, Steineck G, Johansson E, **Rider JR.** Long-term distress after radical prostatectomy versus watchful waiting in prostate cancer: a longitudinal study from the SPCG-4 clinical trial. Eur Urol 2013;64(6):920-8.

37. Pettersson A, Lis RT, Meisner A, Flavin R, Stack EC, Fiorentino M, Finn S, Graff RE, Penney KL, **Rider JR**, Nuttall EJ, Martin NE, Sesso HD, Pollak M, Stampfer MJ, Kantoff PW, Giovannucci EL, Loda M, Mucci LA. Modification of the association between obesity and lethal prostate cancer by TMPRSS2:ERG. J Natl Cancer Inst 2013;105(24):1881-90.

38. Sharma J, Gray KP, Evan C, Nakabayashi M, Fichorova R, **Rider J,** Mucci L, Kantoff PW, Sweeney CJ. Elevated insulin-like growth factor (IGFBP-1) in men with metastatic cancer starting androgen deprivation therapy (ADT) is associated with shorter time to castration resistance and overall survival. Prostate 2014;74(3):225-34.

39. Bill-Axelson A, Holmberg L, Garmo H, **Rider JR,** Taari K, Busch C, Nordling S, Häggman M, Andersson S-O, Spångberg A, Andrén O, Palmgren J, Steineck G, Adami H-O, Johansson J-E. Radical prostatectomy versus watchful waiting in early prostate cancer. New Engl J Med 2014;370(10):932-42.

40. Sharma J, Gray KP, Harshman L, Evan C, Nakabayashi M, Fichorova R, **Rider J,** Mucci L, Kantoff PW, Sweeney CJ. Elevated IL-8, TNFalpha and MCP-1 in men with metastatic prostate cancer starting androgen deprivation therapy (ADT) are associated with shorter time to castration resistance and overall survival. Prostate 2014;74(8):820-8.

41. Markt SC, **Rider JR**, Penney LK, Schumacher FR, Epstein MM, Fall K, Sesso HD, Stampfer MJ, Mucci LA. Genetic variation across C-reactive protein and risk of prostate cancer. Prostate 2014;74(10):1034-42.

42. Siddiqui MM, Wilson KM, Epstein MM, **Rider JR**, Martin NE, Stampfer MJ, Giovannucci EL, Mucci LA. Vasectomy and risk of prostate cancer: a 24-year follow-up study. J Clin Oncol 2014;32(27):3033-8.

43. Flavin R, Pettersson A, Hendrickson WK, Fiorentino M, Finn S, Kunz L, Judson GL, Lis R, Bailey D, Fiore C, Nuttal E, Martin NE, Stack E, Penney KL, **Rider JR**, Sinnott J, Sweeney C, Sesso HD, Fall K, Giovannucci E, Kantoff P, Stampfer M, Loda M, Mucci LA. SPINK1 protein expression and prostate cancer progression. Clin Cancer Res 2014;20(18):4904-11.

44. Markt SC, Valdimarsdottir UA, Shui IM, Sigurdardottir LG, **Rider JR**, Tamimi RM, Batista JL, Haneuse S, Flynn-Evans E, Lockley SW, Szeisler CA, Stampfer MJ, Launer L, Harris T, Smith AV, Gudnason V, Lindstrom S, Kraft P, Mucci LA. Circadian clock genes and risk of fatal prostate cancer. Cancer Causes Control 2014;26(1):25-33.

45. Sigurdardottir LG, Markt SC, **Rider JR**, Haneuse S, Fall K, Schernhammer ES, Tamimi RM, Flyann-Evans E, Batista JL, Launer L, Harris T, Aspelund T, Stampfer MJ, Gudnason V, Czeisler CA, Lockley SW, Valdimarsdottir UA, Mucci LA. Urinary melatonin levels, sleep disruption, and risk of prostate cancer in elderly men. Eur Urol 2015;67(2):191-4.

46. Graff RE, Pettersson A, Lis RT, DuPre N, Jordahl KM, Nuttall E, **Rider JR**, Fiorentino M, Sesso HD, Kenfield SA, Loda M, Giovannucci EL, Rosner B, Nguyen PL, Sweeney CJ, Mucci LA. The TMPRSS2:ERG fusion and response to androgen deprivation therapy for prostate cancer. Prostate 2015;75(9):897-906.

47. **Rider JR,** Fiorentino M, Kelly R, Gerke T, Jordahl K, Sinnott JA, Giovannucci EL, Loda M, Mucci LA, Finn S. Tumor expression of adiponectin receptor 2 and lethal prostate cancer. Carcinogenesis 2015;36(6):639-47.

48. Sinnott JA*, **Rider JR***, Carlsson J, Gerke T, Tyekucheva S, Penney KL, Sesso HD, Loda M, Fall K, Stampfer MJ, Mucci LA, Pawitan Y, Andersson S-O, Andrèn O. Molecular differences in transition zone and peripheral zone prostate tumors. Carcinogenesis 2015;36(6):632-8. (*Authors contributed equally.)

49. Peterson-Dryden S, Medhin H, Kebabonye-Pusoentsi M, Seage G, Suneja G, Kayembe M, Mmalane M, El-Halabi S, Rebbeck T, **Rider J**, Essex M, Lockman S. Cancer incidence following expansion of retroviral treatment in Botswana. PLOS One 2015;10(8):e0135602.

50. Stopsack KH, Ziehr DR, **Rider JR,** Giovannucci EL. Metformin and prostate cancer mortality: a meta-analysis. Cancer Causes Control 2015;27(1):105-13.

51. Montgomery S, Brus O, Hiyoshi A, Cao Y, **Rider J,** Fall K. Childhood exposures among mothers and Hodgkin's lymphoma in offspring. Cancer Epidemiology 2015;39(6):1006-9.

52. Ahearn TU, Pettersson A, Ebot EM, Gerke T, Graff RE, Morais CL, Hicks, JL, Wilson KM, **Rider JR**, Sesso HD, Fiorentino M, Flavin R, Fin S, Giovannucci EL, Loda M, Stampfer MJ, De Marzo AM, Mucci LA, Lotan TL. A prospective investigation of PTEN loss and ERG expression in lethal prostate cancer. J Natl Cancer Inst 2015;108(2).

53. Hurley PJ, Sundi D, Shinder B, Simons B, Hughes RM, Miller RM, Benzon B, Faraj SF, Netto GJ, Vergara IA, Erho N, Daviioni E, Karnes RJ, Yan G, Ewing CM, Isaacs SD, Berman DM, **Rider JR,** Jordahl KM, Mucci LA, Huang J, An S, Park BH, Isaacs WB, Marchionni L, Ross AE, Schaeffer E. Germline variants in asporin vary by race, modulate the tumor microenvironment and are differentially associated with metastatic prostate cancer. Clin Cancer Res 2016;22(2):448-58.

54. Markt SC, Flynn-Evans EE, Valdimarsdottir U, Sigurdardottir LG, Tamimi RM, Batista JL, Haneuse S, Lockley SW, Stampfer M, Wilson KM, Czeisler CA, **Rider JR,** Mucci LA. Sleep duration and disruption and prostate cancer risk: a 23-year prospective study. Cancer Epidemiol

Biomarkers Prev 2016;25(2):302-8

55. Thorgeirsson T, Jordahl KM, Flavin R, Epstein MM, Fiorentino M, Andersson S-O, Andrèn O, **Rider JR**, Mosquera JM, Ingoldsby H, Fall K, Tryggvadottir L, Mucci LA. Intracellular location of BRCA2 protein expression and prostate cancer progression in the Swedish Watchful Waiting Cohort. Carcinogenesis 2016;37(3):262-8.

56. Shui IM, Kolb S, Hanson C, Sutcliffe S, **Rider JR,** Stanford JL. *Trichomonas vaginalis* infection and risk of advanced prostate cancer. Prostate 2016;76(7):620-3.

57. Graff RE, Pettersson A, Lis RT, Ahearn TU, Markt SC, Wilson KM, **Rider JR,** Fiorentino M, Finn S, Kenfield SA, Loda M, Giovannucci EL, Rosner B, Mucci LA. Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. Am J Clin Nutr 2016;37(3):262-8.

58. **Rider JR,** Wilson KM, Sinnott JA, Kelly RS, Mucci LA, Giovannucci EL. Ejaculation frequency and risk of prostate cancer: updated results with an additional decade of follow up. Eur Urol 2016;70(6):974-82.

59. Börnigen D, Tyekucheva S, Wang X, **Rider JR**, Lee G-S, Mucci LA, Sweeney C, Huttenhower C. Computational reconstruction of NFB pathway interaction mechanisms during prostate cancer. PLoS Comput Biol 12(4): e1004820.

60. Davidsson S, Mölling P, **Rider JR,** Unemo M, Karlsson MG, Carlsson J, Andersson SO, Elgh F, Söderquist B, Andrèn O. Frequency and typing of *Propionibacterium acnes* in prostate tissue obtained from men with and without prostate cancer. Infectious Agents and Cancer 2016;11:26.

61. Stopsack KH, Gerke TA, Sinnott JA, Penney KL, Tyekucheva S, Sesso HD, Andersson S-O, Andrèn O, Cerhan JR, Giovannucci EL, Mucci LA, **Rider JR.** Cholesterol metabolism and lethal prostate cancer. Cancer Res 2016;76(16):4785-90.

62. Yang M, Zu K, Mucci LA, **Rider JR,** Fiorentino M, Clinton SK, Loda M, Stampfer MJ, Giovannucci E. Vascular morphology differentiates prostate cancer mortality risk among men with higher Gleason grade. Cancer Causes Control. 2016 Aug; 27(8):1043-7.

63. Sigurdadottir LG, Markt SC, Sigurdsson S, Aspelund T, Fall K, Schernhammer E, **Rider JR,** Launer L, Harris T, Stampfer MJ, Gudnason V, Czeisler CA, Lockley SW, Valdimarsdottir UA, Mucci LA. Pineal glad volume assessed by MRI and its correlation with 6-sulfatoxymelatonin levels among older men. J Biol Rhythms 2016;31(5):461-9.

64. Wilson KM, Markt SC, Fang F, Nordenvall C, **Rider JR,** Ye W, Adami HO, Stattin P, Nyrèn O, Mucci LA. Snus use, smoking and survival among prostate cancer patients. Int J Cancer 2016;139(12):2753-9.

65. Sinnott JA, Peisch S, Tyekucheva S, Gerke TA, Lis RT, **Rider JR,** Fiorentino M, Stampfer MJ, Mucci LA, Loda M, Penney KL. Prognostic utility of a new mRNA expression signature of Gleason score. Clin Can Res 2017;23(1):81-87.

66. Markt SC, Nuttall E, Turman C, Sinnott J, Rimm EB, Ecsedy E, Unger RH, Fall K, Finn S, Jensen

MK, **Rider JR,** Kraft P, Mucci LA. Sniffing out significant "Pee values": genome wide association study of asparagus anosmia. BMJ 2016;155:i6071.

67. Kelly RS, Sinnott JA, **Rider JR,** Ebot EM, Gerke T, Bowden M, Pettersson A, Loda M, Sesso HD, Kantoff PW, Martin NE, Giovannucci EL, Tyekucheva S, Vander Heiden M, Mucci LA. The role of tumor metabolism as a driver of prostate cancer progression and lethal disease: results of a nested case-control study. Cancer Metab 2016;4:22.

68. Pettersson A, Gerke T, Fall K, Pawitan Y, Holmberg L, Giovannucci EL, Kantoff PW, Adami H-O, **Rider JR***, Mucci LA*. The ABC model of prostate cancer: a conceptual framework for the design and interpretation of prognostic studies. Cancer 2017 [In Press]. (*Authors contributed equally and share senior authorship.)

69. Zareba P, Flavin R, Isikbay M, **Rider JR,** Gerke TA, Finn S, Pettersson A, Giunchi F, Unger RH, Tinianow AM, Andersson SO, Andren A, Fall K, Fiorentino M, Mucci LA. Perinural invasion and risk of lethal prostate cancer. Cancer Epidemiol Biomarkers Prev 2017 [In Press].

70. Giunchi F, Jordahl K, Bolito E, Colecchia M, Patriarca C, D'Errico A, Vasuri F, Malvi D, Fornari A, Bonnetti LR, Corti B, Papotti M, DeGiuli P, Loda M, Montrioni R, Fiorentino M, **Rider JR.** Concordance in the histological diagnosis of focal prostatic atrophy lesions, acute and chronic prostatitis, PIN and prostate cancer. Virchows Archiv 2017 [In Press].

71. Pernar CH, Fall K, Rider JR, Pettersson A, Markt SC, Adami H-O, Andersson S-O, Valdimarsdottir U, Mucci LA. A walking intervention among men with prostate cancer: a pilot study. Clin Genitourin Can 2017 [In Press].

72. Ebot EM, Gerke T, Labbe DP, Sinnott JA, Zadra G, Rider JR, Tyekucheva S, Wilson KM, Kelly RS, Shui IM, Loda M, Kantoff PW, Finn S, Vander Heiden MG, Brown M, Giovannucci EL, Mucci LA. Gene expression profiling of prostate tissue identifies chromatin regulation as a potential link between obesity and lethal prostate cancer. Cancer 2017 [In Press].

Book Chapters

1. Mucci LA, Wilson KM, and Rider JR. (2017) Cancer Screening. In Loda M, Mucci LA, Mittelstadt M, Van Hemelrijck M, Cotter MB (Eds), *Pathology and Epidemiology of Cancer*, pp. 73-82. Springer International Publishing.

Other Peer-Reviewed Publications and Editorials

1. **Stark (Rider) JR,** Zhang CS. Investigation of systemic folate status, impact of alcohol intake and levels of DNA damage in mononuclear cells of breast cancer patients [Invited Commentary]. Breast Diseases: A Year Book Quarterly 2006;16(4):332-333.

2. **Stark (Rider) JR,** Mucci LA, Rothman KJ, Adami HO. Screening for prostate cancer remains controversial [Analysis and Comment]. BMJ 2009;339:784-6.

3. **Rider JR.** Trouble in paradise: unmeasured confounding in registry-based studies of etiologic factors [Invited Editorial]. Eur Urol 2016;70(6):974-82.

4. **Rider JR,** Wilson KM, Sinnott JA, Kelly RS, Mucci LA, Giovannucci EL. Reply to Herney Andrés

García-Perdomo and Ramiro Manzano Nunez's Letter to the Editor re: Ejaculation frequency and risk of prostate cancer. Eur Urol 2016;70(6):e156-e157.

5. **Rider JR.** Lead time, like trains and tides, stops for no one [Invited Editorial]. Eur Urol 2017;71(2):202-3.

6. **Rider JR, Wilson KM, Mucci LA, Giovannucci EL.** Reply to Annweiler et al.'s Letter to the Editor re: Ejaculation frequency and risk of prostate cancer. Eur Urol 2016 [In Press].

7. **Rider JR.** Invited commentary re: Nair-Shalliker V et al., Adult body size, sexual history and adolescent sexual development, may predict risk of developing prostate cancer: Results from the New Wales Lifestyle and Evaluation of Risk Study (CLEAR). Practice Update: Urology. February 9, 2017. http://www.practiceupdate.com/content/adult-body-size-sexual-history-and-adolescent-sexual-development-may-predict-risk-of-prostate-cancer/49064/11/0/1

Thesis

Stark (Rider) JR. Biomarkers and Prostate Cancer Mortality. Boston, MA: Harvard School of Public Health;2008.

Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings

1. **Rider JR,** Svensson M, Ohlson A-L, Sandblom D, Andersson S-O, Andrén O. ERG rearrangement status and hormone therapy timing and response. 19th Annual Prostate Cancer Foundation Scientific Retreat, Carlsbad, California, October 25-27, 2012.
2. **Rider JR,** Udesky J, Fiorentino M, Giovannucci EL, Brown M, Mucci LA. The collective role of circulating vitamin D, prostatic vitamin D receptor expression, and inflammation in lethal prostate cancer. Prostate Cancer Foundation Annual Scientific Retreat, National Harbor, Maryland, October 23-26, 2013.
3. **Rider JR**, Sinnott JA, Mucci LA. Differential gene expression in prostate tissue according to ejaculatory frequency. 22nd Annual Prostate Cancer Foundation Scientific Retreat, Washington, D.C., October 8-10, 2015.
4. **Rider JR,** Sinnott JA, Mucci LA. Gene expression in prostate tissue according to history of ejaculation. ASCO Genitourinary Cancers Symposium, San Francisco, California, January 7-9, 2015.
5. **Rider JR**, Wilson KM, Gerke T, Ebot E, Sinnott JA, Mucci LA. Differential gene expression in prostate tissue according to sexual behaviors. American Urological Association Annual Meeting, San Diego California, May 6, 2016.
6. Stopsack K, Gerke T, Giovannucci E, Mucci LA, **Rider JR.** Gene expression of cholesterol transporters and regulators in aggressive prostate cancer. EMBO Translational Research in Cancer Cell Metabolism Conference, Bilbao, Spain, October 3-5, 2016.

Narrative Report

My primary research interests are in prostate cancer epidemiology and the identification of patient and tumor characteristics that could reduce overdiagnosis and overtreatment. Collaborating with research pathologists, urologists, medical oncologists, molecular biologists, immunologists, virologists, and bioinformaticists, I have utilized data from a large Swedish population-based studies (CaPS and PCBaSe) and a Swedish randomized trial (SPCG-4), Swedish clinical cohorts, the Physicians' Health Study, and

the Health Professionals Follow-up Study. In 2013 I was awarded the Prostate Cancer Foundation Young Investigator Award and a fellowship from Harvard Medical School's Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine for projects that aim to identify translatable knowledge around the vitamin D pathway in aggressive prostate cancer.

As a post-doctoral fellow at the Harvard T.H. Chan School of Public Health and the Channing Laboratory, I focused on biomarkers primarily involved in infection and inflammation using germ-line, plasma and tissue specimens. I received a Career Development Award from the Dana Farber/Harvard Cancer Center Prostate Cancer SPORE to conduct a tissue-based study of predictors and outcomes associated with post-atrophic hyperplasia, a type of focal prostate atrophy hypothesized to be a regenerative lesion and prostate cancer precursor. This initial grant led to other opportunities to pursue the role inflammation and atrophy in tissue specimens, including an A. David Mazzone Career Development Award to study pre-diagnostic tissue characteristics that predict overall and lethal prostate cancer in benign specimens. In 2009 I was a visiting researcher in the Department of Urology at Örebro University Hospital in Sweden. In this role I had exposure to the clinical aspects of prostate cancer diagnosis and treatment, abundant opportunities to design and implement new observational and randomized studies, and valuable experience working with new datasets, including Swedish registry data.

Through collaborations with Swedish and US-based investigators, I am expanding my research focus to study the role of infections on various malignancies. I am involved in ongoing studies of HPV infection in penile carcinoma and tumors of the head and neck, as well as the role of the oral microbiome in cancer. Moreover, I am pursuing projects that investigate malignancies in HIV-infected populations, including a study to shed light on the consistently lower incidence of prostate cancer in HIV-positive compared to HIV-negative men.

In addition to my research pursuits, I supported the educational mission of the Harvard Chan School through a secondary Assistant Professor appointment in the Department of Epidemiology. I taught *Infections and Cancer*, a course recognized by the Chan School Committee on Educational Policy for its high overall rating by students for three consecutive years. In fall 2014 I began leading a second course, *Cancer Prevention*. I contributed to the MPH program in Clinical Effectiveness by leading a workshop in *Introduction to Clinical Epidemiology* and supervising student practicum projects. In 2015 I served on the Mentoring Committee of the MPH-EPI program, a partially online program for MDs pursuing population-based research training, and acted as Co-Chair for the Chan School Department of Epidemiology Admissions Committee. I continue to mentor students at the Chan School in my role as Adjunct Assistant Professor. In my current position at the Boston University School of Public Health, I teach Intermediate Epidemiology Methods and am developing a new cancer epidemiology course. I also serve on BUSPH MPH Admissions Committee.

Exhibit B

Materials Considered List

1. Acquavella, J. et al., *Exposure Misclassification in Studies of Agricultural Pesticides*, 17 Epidemiology 69 (2006).

2. Acquavella, J. et al., *Glyphosate Biomonitoring for Farmers and Their Families: Results from the Farm Family Exposure Study*, 112 Envtl. Health Persp. 321 (2004).

3. Agu, V. et al., *Geographic Patterns of Multiple Myeloma: Racial and Industrial Correlates, State of Texas, 1969-71*, 65 J. Nat'l Cancer Inst. 735 (1980).

4. Ahn, R. et al., *Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study*, 356 BMJ (2017).

5. Alavanja, M. et al., *Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study*, 9 PLoS One e109332 (2014).

6. Alavanja, M. et al., *The Agricultural Health Study*, 104 Envtl. Health Persp. 362 (1996).

7. Alavanja, M. et al., *Cancer Incidence in the Agricultural Health Study*, 31 suppl 1 Scandinavian J. Work Env't & Health 39 (2005).

8. Alavanja, M. et al., *DRAFT-Lymphoma risk and pesticide use in the Agricultural Health Study* (Mar. 15, 2013) (unpublished study) (on file with Authors).

9. Alavanja, M. et al. *Lymphoma risk and pesticide use in the Agricultural Health Study*, Unpublished manuscript (2013).

10. American Cancer Society, *Types of Non-Hodgkin Lymphoma*, https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html (accessed May 24, 2017).

11. Anscombe, F., *The Summarizing of Clinical Experiments by Significance Levels*, 9 Statistics in Medicine 703 (1990).

12. Arbuckle, T. et al., *Predictors of Herbicide Exposure in Farm Applicators*, 75 Int'l Archives Occupational Envtl. Health 406 (2002).

13. Aspelin, A. & A. Grube, *Pesticides Industry Sales and Usage 1996 and 1997 Market Estimates*, U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances (1999).

14. Aspelin, A., *Pesticides Industry Sales and Usage 1994 and 1995 Market Estimates*, Office of Prevention, Pesticides and Toxic Substances (1997).

15. Battaglin, W. et al., *Glyphosate and Its Degradation Product AMPA Occur Frequently and Widely in U.S. Soils, Surface Water, Groundwater, and Precipitation*, 50 J American Water Resources Ass'n 275 (2014).

16. Bekelman, J. et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research*, 289 JAMA 454 (2003).

17. Berkson, J., *Tests of significance considered as evidence*, 32 Int'l. J. Epidemiology 687 (2003).

18. BfR, *Assessment of IARC Monographies Volume 112 (2015); Glyphosate*, Renewal Assessment Report: Glyphosate Addendum I to RAR (2015).

19. Blair, A. & D. White, *Death Certificate Study of Leukemia Among Farmers From Wisconsin*, 66 J. Nat'l Cancer Inst. 1027 (1981).

20. Blair, A. & D. White, *Leukemia Cell Types and Agricultural Practices in Nebraska*, 10 Archives Envtl. Health 211 (1985).

21. Blair, A. & L. Freeman, Ph.D., *Epidemiologic Studies of Cancer in Agricultural Populations: Observations and Future Directions*, 14 J. Agromedicine 125 (2009).

22. Blair, A. & S. Zahm, *Patterns of Pesticide Use among Farmers: Implications for Epidemiologic Research*, 4 Epidemiology 55 (1993).

23. Blair, A. et al., *Guidelines for Application of Meta-analysis in Environmental Epidemiology*, 22 Regulatory Toxicology and Pharmacology 189 (1995).

24. Blair, A. et al., *Reliability of Reporting on Life-Style and Agricultural Factors by a Sample of Participants in the Agricultural Health Study from Iowa*, 13 Epidemiology 94 (2002).

25. Blettner, M. et al., *Traditional reviews, meta-analyses and pooled analyses in epidemiology*, 28 Int'l. J. Epidemiology 1 (1999).

26. Bonner, M. et al., *Occupational Exposure to Pesticides and the Incidence of Lung Cancer in the Agricultural Health Study*, 125 Envtl. Health Persp. 544 (2017).

27. Bosch, F. & S. de Sanjosé, *Chapter 1: Human papillomavirus and cervical cancer—burden and assessment of causality*, 31 J. Nat'l. Cancer Inst. Monographs 3 (2003).

28. Bradford Hill, A., *The Environment and Disease: Association or Causation?*, 58 Proc R Soc Med 295 (1965).

29. Bravata, D. & I. Olkin, *Simple Pooling Versus Combining in Meta-Analysis*, 24 Evaluation & The Health Professionals 218 (2001).

30. Bridger, R. & P. Sparto, *Spade design, lumbar motions, risk of low-back injury and digging posture*, 1 Occupational Ergonomics 157 (1998).

31. Brown, L. et al., *Pesticide Exposures and Other Agricultural Risk Factors for Leukemia among Men in Iowa and Minnesota*, 50 Cancer Res 6585 (1990).

32. Brown, L. et al., *Pesticide exposures and multiple myeloma in Iowa men*, 4 Cancer Causes & Control 153 (1993).

33. Brusick, D. et al., *Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethy/phosphonic Acid*, 46 Critical Rev Toxicology 56 (2016).

34. Buesching, D. & L. Wollstadt, *Letters to the Editor Cancer Mortality Among Farmers*, 72 J. Nat'l Cancer Inst. 503 (1984).

35. Burmeister, L. et al., *Leukemia and Farm Practices in Iowa*, 115 Am. J. Epidemiology 720 (1982).

36. Burmeister, L. et al., *Selected Cancer Mortality and Farm Practices in Iowa*, 118 Am. J. Epidemiology 72 (1983).

37. Burmeister, L., *Cancer Mortality in Iowa Farmers, 1971-78*, 66 J. Nat'l Cancer Inst. 461 (1981).

38. Cancer Research UK (2016) Cancer incidence by age. https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-zero

39. Cantor, K. & A. Blair, *Farming and Mortality From Multiple Myeloma: A Case-Control Study with the Use of Death Certificates*, 72 J. Nat'l Cancer Inst. 251 (1984).

40. Cantor, K. et al., *Pesticides and Other Agricultural Risk Factors for Non-Hodgkin's Lymphoma among Men in Iowa and Minnesota*, 52 Cancer Res. 2447 (1992).

41. Cantor, K., *Farming and Mortality from Non-Hodgkin's Lymphoma: A Case-Control Study*, 29 Int'l J. Cancer 239 (1982).

42. Chang, E. & E. Delzell, *Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma*, Exponent (2017).

43. Chang, E. & E. Delzell, *Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers*, 0 J. Envtl. Sci. & Health 1 (2016).

44. Coble, J. et al., *Prevalence of exposure to solvents, metals, grain dust, and other hazards among farmers in the Agricultural Health Study*, 12 J. Exposure Analysis & Envtl. Epidemiology 418 (2002).

45. Cocco, P. et al., *Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study*, 70 Occupational & Envtl. Med. 91 (2013).

46. Coupe, R. & P. Capel, *Trends in pesticide use on soybean, corn and cotton since the introduction of major genetically modified crops in the United States*, 72 Pest Management Science 1013 (2016).

47. Cox, C., *Glyphosate Fact Sheets: Part 1, Toxicology; Part 2, Human Exposure and Ecological Effects.* 15(3 and 4) J. Pesticide Reform 1 (1995).

48. Curwin, B. et al., *Urinary Pesticide Concentrations Among Children, Mothers and Fathers Living in Farm and Non-Farm Households in Iowa*, 51 Annals Occupational Hygiene 53 (2007).

49. Dancik, B., *Importance of Peer Review*, The Serials Librarian (1991).

50. De Roos, A. et al., *An Application of Hierarchical Regression in the Investigation of Multiple Paternal Occupational Exposures and Neuroblastoma in Offspring*, 39 Am. J. of Indus. Med. 477 (2001).

51. De Roos, A. et al., *Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study*, 113 Envtl. Health Persp. 49 (2005).

52. De Roos, A. et al., *Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men*, 60 Occupational & Envtl. Med. 1 (2003)

53. Delzell, E. & S. Grufferman, *Mortality Among White and Nonwhite Farmers in North Carolina, 1976-1978*, 121 Am. J. Epidemiology 391 (1985).

54. Dong, J., *Simpson's Paradox*, Encyclopedia of Biostatistics 4108 (1998).

55. Dreiher, J. & E. Kordysh, *Non-Hodgkin Lymphoma and Pesticide Exposure: 25 Years of Research*, 116 Acta Haematologica 153 (2006).

56. Dubrow, R. et al., *Farming and malignant lymphoma in Hancock County, Ohio*, 45 British J. Indus. Med. 25 (1988).

57. Engel, L. et al., *Validity Study of Self-Reported Pesticide Exposure Among Orchardists*, 11(5) J Exposure Analysis Envtl. Epidemiology 359 (2001).

58. EPA, Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, *Cancer Assessment Document – Evaluation of the Carcinogenic Potential of Glyphosate* (Final Report October 1, 2015).

59. EPA, *Glyphosate: Reregistration Eligibility Decision (RED) Facts*, (Sept. 1993).

60. EPA, Letter from Robert J. Taylor, Product Manager, Fungicide-Herbicide Branch, Registration Division on Roundup: EPA Reg. No. 524-308 to Mr. Hannah, Monsanto Co. (Dec. 22, 1975).

61. EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, Regulations.gov (September 12, 2016).

62. Eriksson, M. et al., *Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis*, 123 Int'l J. of Cancer 1657 (2008).

63. European Food Safety Authority, *Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate*, 13 EFSA J. 4302 (2015).

64. Evans, S. et al., *The end of the p value?* 60 British Heart J. 177 (1988).

65. Expert Report of Alfred I. Neugut, MD, PHD In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).

66. Expert Report of Dr. Beate Ritz, M.D., Ph.D. In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).

67. Expert Report of Dr. Christopher J. Portier In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).

68. Expert Report of Dr. Dennis Weisenburger, M.D. In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).

69. Expert Report of Dr. Chadi Nabhan In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).

70. Fasal, E. et al., *Leukemia and Lymphoma Mortality and Farm Residence*, 87 Am. J. Epidemiology 267 (1968).

71. Feng, J. & D. Thompson, *Fate of Glyphosate in a Canadian Forest Watershed. 2. Persistence in Foliage and Soils*, 38 J. Agricultural Food Chemistry 1118 (1990).

72. Flower, K. et al., *Cancer Risk and Parental Pesticide Application in Children of Agricultural Health Study Participants*, 112 Envtl. Health Persp. 631 (2004).

73. Freeman, L. et al., *Poultry and Livestock Exposure and Cancer Risk among Farmers in the Agricultural Health Study*, 23 Cancer Causes Control 663 (2012).

74. Fritschi, L. et al., *Occupational Exposure to Pesticides and Risk of Non-Hodgkin's Lymphoma*, 162 Am. J. Epidemiology 849 (2005).

75. Gallagher, R. et al., *Cancer and Aplastic Anemia in British Columbia Farmers*, 72 J. Nat'l Cancer Inst. 1311 (1984).

76. Gelman, A. & E. Loken, *The Statistical Crisis in Science*, 102 American Scientist 460 (2014).

77. Gelman, A. & H. Stern, *The Difference Between "Significant" and "Not Significant" is not Itself Statistically Significant*, 60 The American Statistician 328 (2006).

78. Geng, Z., *Collapsibility of Relative Risk in Contingency Tables with a Response Variable*, 54 J. Royal Statistical Society. Series B (Methodological) 585 (1992).

79. Gigerenzer, G., *Mindless Statistics*, 33 J. Socio-Economics 587 (2004).

80. Glass, G., *Primary, Secondary, and Meta-Analysis of Research 1*, 5 Educational Researcher 3 (1976).

81. Goldsmith, J. & T. Guidotti, *Environmental Factors in the Epidemiology of Lymphosarcoma*, 12 Pathology Ann. 411 (1977).

82. Good, I. & Y. Mittal, *The Amalgamation and Geometry of Two-By-Two Contingency Tables*, 15 The Annals of Statistics 694 (1987).

83. Goodman, S., *Toward Evidence-Based Medical Statistics. 1: The P Value Fallacy*, 130 Annals of Internal Medicine 995 (1999).

84. Green, M. et al., *Reference Guide on Epidemiology In: Reference Manual on Scientific Evidence: Third Edition*, The National Academies Press 597 (2011).

85. Greenland, S., *Nonsignificance Plus High Power Does Not Imply Support for the Null Over the Alternative*, 22 Annals of Epidemiology 364 (2012).

86. Grieve, A., *How to test hypotheses if you must*, 14 Pharmaceutical Statistics 139 (2015).

87. Grube, A. et al., *Pesticides Industry Sales and Usage 2006 and 2007 Market Estimates*, U.S. Environmental Protection Agency, Office of Pesticide Programs (2011).

88. Guyton, K. et al., *Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon, and* Glyphosate, 16 Lancet Oncology 490 (2015).

89. Hardell, L. & M. Eriksson, *A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides*, 85 Cancer 1353 (1999).

90. Hardell, L. et al., *Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies*, 43 Leukemia and Lymphoma 1043 (2002).

91. Hardell, L. et al., *Malignant Lymphoma and Exposure to Chemicals, Especially Organic Solvents, Chlorophenols and Phenoxy Acids: A Case-Control Study*, 43 Br. J. Cancer 169 (1981).

92. Hardell, L., *Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents*, 7 Scandinavian Journal of Work, Env't & Health 119 (1981).

93. Hernán, M. et al., *A structural approach to selection bias*, 15 Epidemiology 615 (2004).

94. Hoar, S. et al., *Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma*, 256 JAMA 1141 (1986).

95. Hoekstra, R. et al., *Probability as certainty: Dichotomous thinking and the misuse of p values*, 13 Psychonomic Bulletin & Review 1033 (2006).

96. Hofmann, J. et al., *Farm Characteristics, Allergy Symptoms, and Risk of Non-Hodgkin Lymphoid Neoplasms in the Agricultural Health Study*, 24 Cancer Epidemiology Biomarkers & Prevention 587 (2015).

97. Hohenadel, K. et al., *Exposure to Multiple Pesticides and Risk of Non-Hodgkin Lymphoma in Men from Six Canadian Provinces*, 8 Int'l J. Envtl. Res. & Public Health 2320 (2011).

98. Hoppin, J. et al., *Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study*, 12 J. Exposure Analysis & Envtl. Epidemiology 313 (2002).

99. Howe, G. & J. Lindsay, *A Follow-up Study of a Ten-Percent Sample of the Canadian Labor Force. I. Cancer Mortality in Males, 1965-73*, 70 J. Nat'l Cancer Inst. 37 (1983).

100. International Agency for Research on Cancer (IARC), Monograph Vol. 112 on the Evaluation of Carcinogenic Risks to Humans, *Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos* (2015).

101. Jauhiainen, A. et al., *Occupational Exposure of Forest Workers to Glyphosate During Brush Saw Spraying Work*, 52 American Industrial Hygiene Ass'n J 61 (1991).

102. JMPR, *Pesticide residues in food – 2004: Toxicological evaluations – Toxicological Monographs and Monograph Addenda*, Joint FAO/WHO Meeting on Pesticide Residues (2006).

103. Kachuri, L. et al., *Multiple pesticide exposures and the risk of multiple myeloma in Canadian men*, 133 Int'l J. Cancer 1846 (2013).

104. Kaye, D., *Is Proof of Statistical Significance Relevant?* 61 Washington Law Review 1333 (1986).

105. Koutros, S. et al., *An Update of Cancer Incidence in the Agricultural Health Study*, 52 J. Occupational & Envtl. Med. 1098 (2010).

106. Landgren, O. et al., *Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study*, 113 Blood 6386 (2009).

107. Lash, T., *Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty*, 2 J. Occupational Med. Toxicology 1 (2007).

108. Lecoutre, M. et al., *Even statisticians are not immune to misinterpretations of Null Hypothesis Significance Tests*, 38 Intl J. Psychology (2003).

109. Lee, W. et al., *Non-Hodgkin's Lymphoma Among Asthmatics Exposed to Pesticides*, 111 Intl. J. Cancer 298 (2004).

110. Lew, M., *Bad statistical practice in pharmacology (and other basic biomedical disciplines): you probably don't know P*, 166 British J. Pharmacology 1559 (2012).

111. Lukaszewicz-Hussain, A., *Role of Oxidative Stress in Organophosphate Insecticide Toxicity-Short Review*, 98 Pesticide Biochemistry and Physiology 145 (2010).

112. Maeda, K. et al., *Low Back Pain Related to Bowing Posture of Greenhouse Farmers*, 9 J. Human Ergology 117 (1980).

113. Matthews, J. & D. Altman, *Statistics Notes- Interaction 2: compare effect sizes not P values*, 313 British J. Pharmacology 808 (1996).

114. McDuffie, H. et al., *Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health*, 10 Cancer Epidemiology, Biomarkers & Prevention 1155 (2001).

115. Melbye, M. et al., Testbook of Cancer Epidemiology 669-693 (H.O. Adami et al. eds., 2nd ed. 2008).

116. Milham, S., *Leukemia and Multiple Myeloma in Farmers*, 94 Am. J. Epidemiology 307 (1971).

117. Mink, P. et al., *Epidemiologic studies of glyphosate and cancer: A review*, 63 Reg. Toxicology and Pharmacology 440 (2012).

118. Mink, P. et al., *Epidemiologic Studies of Glyphosate and Non-Cancer Health Outcomes: A Review*, 61 Regulatory Toxicology Pharmacology 172 (2011).

119. Mittal, Y., *Homogeneity of Subpopulations and Simpson's Paradox*, 86 J. American Statistical Association 167 (1991).

120. Montgomery, M. et al., *Characteristics of non-participation and potential for selection bias in a prospective cohort study*, 53 Am. J. Indus. Med. 486 (2010).

121. Morabia, A. et al., *Smoking Prevalence in Neighborhood and Hospital Controls: Implications for Hospital-Based Case-Control Studies*, 49 J. Clinical Epidemiology 885 (1996).

122. Morton, L. et al., *Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph non-Hodgkin lymphoma subtypes project*, 48 J. National Cancer Institute Monographs 130 (2014).

123. Myers, J. et al., *Concerns over Use of Glyphosate-Based Herbicides and Risks Associated with Exposures: A Consensus Statement*, 15 Envtl. Health 19 (2016).

124. National Cancer Institute, *Cancer Stat Facts: Non-Hodgkin Lymphoma* https://seer.cancer.gov/statfacts/html/nhl.html (accessed May 24, 2017).

125. Neupane, B. et al., *Community controls were preferred to hospital controls in a case-control study where the cases are derived from the hospital*, 63 J. Clinical Epidemiology 926 (2010).

126. Newton, M. et al., *Fate of Glyphosate in an Oregon Forest Ecosystem*, 32 J. Agricultural Food Chemistry 1144 (1984).

127. Niemann, L. et al., *A Critical Review of Glyphosate Findings in Human Urine Samples and Comparison with the Exposure of Operators and Consumers*, 10 J. Fur Verbraucherschutz and Lebensmittelsicherheit 3 (2015).

128. Nordstrom, M. et al., *Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukemia evaluated in a case-control study*, 77 Brit. J. of Cancer 2048 (1998).

129. Occupational Cancer Research Centre, *An Detailed Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma in the North American Pooled Project (NAPP)*, (June 3, 2015).

130. Orsi, L. et al., *Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study*, 66 Occupational and Envtl. Med. 291 (2009).

131. Pahwa, M. et al., *A detailed assessment of glyphosate use and the risks of non-Hodgkin lymphoma overall and by major histological sub-types: findings from the North American Pooled Project*, Occupational Cancer Research Centre (June 10, 2016).

132. Pahwa, M. et al., *An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project*, Occupational Cancer Research Centre (August 31, 2015).

133. Pahwa, M. et al., *An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP)* (Sept. 21, 2015) (unpublished article).

134. Pahwa, M. et al., *An Evaluation of Glyphosate Use and the Risks of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project (NAPP)*, Envtl. Health Persp. (2015).

135. Pahwa, M., *The North American Pooled Project (NAPP): Pooled Analyses of Case-Control Studies of Pesticides and Agricultural Exposures, Lymphohematopoietic Cancers and Sarcoma*, BMJ (2014).

136. Pearce, N. et al., *IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans.* 123 Envtl. Health Persp. 507 (2015).

137. Pearce N. et al, *Malignant Lymphoma and Multiple Myeloma Linked with Agricultural Occupations in a New Zealand Cancer Registry-Based Study,* 121 Am. J. Epidemiology 225 (1985).

138. Perry, A. et al., *Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project*, 101 Haematologica 1244 (2016).

139. Poole, C., *Beyond the Confidence Interval*, 77 American J. Public Health 195 (1987).

140. Portier, C. et al., *Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)*, 70 J Epidemiology Community Health 741 (2016).

141. Presutti, R. et al., *Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project*, Int'l J. Cancer (2016).

142. Riihimaki, H., *Low-back pain, its origin and risk indicators*, 17 Scandinavian J. Work Env't. Health 81 (1991).

143. Rinsky, J. et al., *Assessing the Potential for Bias From Nonresponse to a Study Follow-up Interview: An Example From the Agricultural Health Study*, American Journal of Epidemiology (2017).

144. Rose, G., *Sick Individuals and Sick Populations*, 14 Intl. J. Epidemiology 32 (1985).

145. Rozeboom, W., *The Fallacy of the Null-Hypothesis Significance Test*, 57 Psychological Bulletin 416 (1960).

146. Ruano-Ravina, A. et al., *Population-based versus hospital-based controls: are they comparable?*, 22 Gaceta Sanitaria 609 (2008).

147. Sadetzki, S. et al., *The limitations of using hospital controls in cancer etiology – one more example for Berkson's bias*, 18 European J. Epidemiology 1127 (2003).

148. Salsburg, D., *The Religion of Statistics as Practiced in Medical Journals*, 39 The American Statistician 220 (1985).

149. Samuels, M., *Simpson's Paradox and Related Phenomena*, 88 J. American Statistical Association 81 (1993).

150. Schinasi, L. & M. Leon, *Non-Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta-Analysis*, 11 Int'l J. Envtl. Res. & Public Health 4449 (2014).

151. Schumacher, M., *Farming Occupations and Mortality from Non-Hodgkin's Lymphoma in Utah*, 27 J. Occupational Med. 580 (1985).

152. SEER Cancer Statistics Review, 1975-2013. Table 19.7: Non-Hodgkin Lymphoma, Incidence and mortality rates by age. 2016; https://seer.cancer.gov/archive/csr/1975_2013/results_merged/sect_19_nhl.pdf

153. Shamseer, L. et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation*, 349 BMJ (2015).

154. Simpson, E., *The Interpretation of Interaction in Contingency Tables*, 13 J. Royal Statistical Society. Series B (Methodoligical) 238 (1951).

155. Solomon, K. et al., *Human Health and Environmental Risks from the Use of Glyphosate Formulations to Control the Production of Coca in Colombia: Overview and Conclusions*, 72(15-16) J. Toxicology Envtl. Health A 914 (2009).

156. Solomon, K., *Glyphosate in the General Population and in Applicators: A Critical Review of Studies on Exposures*, 46 Critical Rev Toxicology 21 (2016).

157. Sorahan, T., *Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data*, 12 Int'l J. Envtl. Res. & Public Health 1548 (2015).

158. Stark, J. et al, *Toll-like Receptor Signaling Pathway Variants and Prostate Cancer Mortality*, 18 Cancer Epidemiology Biomarkers Prevention 1859 (2009).

159. Sterne, J., *Sifting the evidence-what's wrong with significance tests?*, 322 British Medical J. 226 (2001).

160. Stroup, D. et al., *Meta-analysis of Observational Studies in Epidemiology*, 283 JAMA 2008 (2000).

161. Szklo, M. & J. Nieto, *Epidemiology: Beyond the Basics* 165-167 (3d ed. 2014).

162. Tarone, R., *On the International Agency for Research on Cancer Classification of Glyphosate as a Probable Human Carcinogen*, 0 European J. Cancer Prevention 1 (2016).

163. The International Agency for Research on Cancer [IARC], *List of Participants*, Vol. 112 (Mar. 3-10, 2015).

164. Thompson, B., *The "significance" crisis in psychology and education*, 33 J. Socio-Economics 607 (2004).

165. Trafimow, D. & M. Marks, *Editorial*, 37 Basic and Applied Social Psychology 1 (2015).

166. Van Tulder, M. et al., *Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group*, 28 Spine 1290 (2003).

167. Varona, M. et al., *Effects of Aerial Applications of the Herbicide Glyphosate and Insecticides on Human Health*, 29 Biomedica 456 (2009).

168. Videotaped Deposition of Aaron Earl Blair, Ph.D., In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. Mar. 20, 2017).

169. Waddell, B. et al., *Agricultural use of organophosphate pesticides ad the risk of non-Hodgkin's lymphoma among male farmers (United States)*, 12 Cancer Causes and Control 509 (2001).

170. Walker, A., *Reporting the Results of Epidemiologic Studies*, 76 American J. Public Health 556 (1986).

171. Walker, E. et al., *Meta-analysis: Its strength and limitations*. 75 Cleveland Clinic Journal of Medicine 53 (2008).

172. Weber, J. et al., *Étude de l'exposition professionnelle des travailleurs forestiers exposés au glyphosate*, Centre de Toxicologie du Québec (1988).

173. Weichenthal, S. et al., *A Review of Pesticide Exposure and Cancer Incidence in the Agricultural Health Study Cohort*, 118 Envtl. Health Persp. 1117 (2010).

174. Weisenburger, D., *Environmental Epidemiology of Non-Hodgkin's Lymphoma in Eastern Nebraska.* 18 Am J. Indus. Med 303 (1990).

175. Weisenburger, D., *Lymphoid Malignancies in Nebraska: A Hypothesis*, 70 Neb. Med. J. 300 (1985).

176. Weisenburger, D., *Pathological Classification of Non-Hodgkin's Lymphoma for Epidemiological Studies*, 52 Cancer Res 5456s (1992).

177. Wigle, D. et al., *Mortality Study of Canadian Male Farm Operators: Non-Hodgkin's Lymphoma Mortality and Agricultural Practices in Saskatchewan*, 82 J. Nat'l Cancer Institute 575 (1990).

178. Wiklund, K. et al., *A Swedish cancer-environment register available for research*, 7 Scandinavian J. Work Env't & Health 64 (1981).

179. Williams, G. et al., *Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review*, *46* Crit Rev Toxicology 44 (2016).

180. Williams, R. et al., *Associations of Cancer Site and Type With Occupation and Industry From the Third National Cancer Survey Interview*, 59 J. Nat'l Cancer Inst. 1147 (1977).

181. Woodburn, A., *Glyphosate: production, pricing and use worldwide*, 56 Pest Management Science 309 (2000).

182. World Health Organization, *Epidemiology*, http://www.who.int/topics/epidemiology/en/ (accessed May 22, 2017).

183. Yates, W. et al., *Drift of Glyphosate Sprays Applied with Aerial and Ground Equipment*, 26 Weed Science 597 (1978).

184. Zahm, S. et al., *A Case-Control Study of Non-Hodgkin's Lymphoma and the Herbicide 2,4-Dichlorophenozyacetic Acid (2,4-D) in Eastern Nebraska*, 1 Epidemiology 349 (1990).

185. Zhang, C. et al., *Health effect of agricultural pesticide use in China: implications for the development of GM crops*, Scientific Reports (2016).