

CUTT

# A Healthy Ecosystem

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## Exposure ⇨ Cancer:

### What Does it Take to Show Cause and Effect?

**F**ollowing the recent publication of findings from the Long Island Breast Cancer Study, a number of newspapers and magazines published articles and commentaries about the importance and impact of this study. (For more information, see the study's website: <http://www.cancer.gov/cancerinfo/LIBCSP>.)

Whether they approved or disapproved of the study, these articles generally overestimated the impact of a single study. Most of the articles about the study gave the impression that the results of a single study can determine if there is a cause-and-effect relationship between exposure to a specific chemical and changes in breast cancer risk. Some of these articles even went so far as to suggest that this single study provided conclusive evidence about the cause-and-effect relationship between all environmental contaminants and breast cancer.

Missing from most of this coverage was the placement of this article in the context of how epidemiological cause-and-effect relationships are established and the contribution of a single study to an understanding of this relationship. We hope to clarify these issues by describing the scientific evidence that is need before a cause-and-effect relationship can be established.

#### The Long Island Study

This recently reported part of the Long Island Breast Cancer Study was conducted to determine whether there was an association between women's blood levels of various organochlorine toxins and their risk of getting breast cancer. An association (which was not found) would have shown that there was a connection or linkage between the event (exposure) and the disease (breast cancer) and that this association would not be expected to have occurred by chance.

But the finding of an association, however strong, does not necessarily mean that the exposure causes the disease. An example of this involves the epidemiology of the birth of children with Down's syndrome. In this case, there is a strong association between the risk of a child having Down's syndrome and the child having a late birth order (being born late into the family and having a number of older siblings). Yet the cause of Down's syndrome is the addition of an extra copy of chromosome number 21. The association of Down's syndrome with birth order is observed because this extra chromosome occurs more frequently in older women,

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The Long Island Breast Cancer Study Project

## Cancer Cause-and-Effect

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and the mothers of children late in the birth order are usually older. Being a later child does not cause the syndrome, it is only associated with it through the connection with older mothers.

### Causality

Determination of a cause-and-effect relationship for a disease, or as it is frequently called in epidemiological circles, causality, is arrived at by the evaluation of the results from a large number of studies of the epidemiology as well as the basic biology of the disease. A set of standards for assessing causality were first formally set forth by a panel organized by the US Surgeon General during the 1960's. These standards established a set of experimental results which should be met to conclude that there is a cause-and-effect relationship between an event (exposure) and formation of a disease. Evaluation of how well these standards are met allow for determination of the strength of the evidence for exposure and disease associations. The standards are now known as the criteria for causality. Described below are the criteria for causality evidence for a cause-and-effect relationship between an exposure and a disease.

- Consistency of the association: The results of most studies agree using different methods and examining different groups of people.
- Strength of the association: The associated risk is strong enough to meaningfully affect the occurrence of the disease in real-life settings.
- Dose relationship for the association: There is a clear trend in the size of the risk of the disease that increases (or decreases) with the extent of exposure.
- Plausibility of the association: The biological effects of the exposure can be sensibly related to formation of the disease.
- Time of exposure for the association: The time between the exposure and occurrence of the disease agrees with the time required for development of the disease.

The following sections will discuss the key elements of these criteria. This discussion will use as an example the association between alcohol consumption and breast cancer risk. Alcohol consumption was chosen as an example because it is generally accepted to be associated (albeit moderately) with breast cancer risk.

### Consistency of the Association

If there is a cause-and-effect relationship, it is expected that the results of most studies will be consistent. But a frustration frequently encountered by both scientists and nonscientists alike is the inconsistency of the results of studies examining the association of various exposures to the risk of various types of cancer. It is not unusual to find conflicting results. Some studies may report no association or a negative association between an environmental exposure and cancer risk while other studies may report a positive association with cancer risk. A number of factors produce these inconsistencies. The major contributing factors include the relatively low risk associated with many "environmental" exposures, the difficulty of accessing exposure due to the long period of time required for cancer development, and differences in experimental design (discussed below in more detail).

This lack of consistency provides a good example of the necessity for good scientific judgement in the evaluation of evidence. In many cases inconsistency arises from weakness in the study design. The best studies a) look at a large number of women who are representative of the larger population, b) accurately measure their exposure and when it may have occurred, c) account for the contribution of established risk factors to the breast cancer observed, and d) use a comparison (control) group of women who ideally differ only in the presence of the disease.

In addition, studies that collect information from healthy women and subsequently follow them over time for the occurrence of the disease are considered to have less chance for bias. In some cases, elimination of weaker studies that do not meet these good design characteristics, will resolve the inconsistency of association across studies. However, the size of the change in risk commonly seen with environmental exposures is also a contributor to this inconsistency. Thus, consistency would only be expected between studies examining a large number of women.

For example, there is consistency in the results of the many studies examining alcohol consumption and breast cancer risk. Out of 35

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studies (of various designs and conducted in various countries), 26 found an increase in risk for women who drank the most. Nonetheless, 7 studies reported no effect of alcohol consumption on breast cancer risk and 2 studies reported a decrease in risk. This amount of inconsistency is not surprising considering the size of the risk associated with this exposure. There is about a 40% increase in the relative risk of breast cancer for women who have about 4 drinks daily. Nonetheless, the association of alcohol consumption with breast cancer risk is considered to be one of the most consistent of the dietary factors contributing to breast cancer risk.

**Strength of the Association**

The criteria for causality also predict that there will be a strong association between exposure and disease when there is a cause-and-effect relationship. The term “strong” must be seen as a relative one in this context and the values for “environmental” exposures are viewed accordingly.

Individual “environmental” exposures have not been associated with large increases in breast cancer risk. But it is important to realize that epidemiological studies use the term “environmental” exposures as a broad catch phrase to include exposures from air, water and food, as well as lifestyle, such as smoking and drinking. This is not to imply that these “environmental” exposures do not have a substantial contribution to the incidence of breast cancer.

The most accurate studies examining the contribution of environmental factors to breast cancer risk were conducted examining the differences in cancer diagnosis between identical and nonidentical twins. This recent large study of twins in Sweden, Denmark and Finland (547 pairs of identical twins and 1075 pairs of non-identical twins) reported that about three quarters of all risk for breast cancer was due to environmental exposures. The low level of risk seen for individual environmental exposures is possibly due to differences in susceptibility between women and to the individual environmental

exposures acting through interactions between themselves and with other factors rather than alone.

Typically, in evaluating the strength of “environmental” associations, changes in risk less than 20% are viewed as suspect. Statistical significance of the results is needed to assure that they are not due to chance alone. The risk of lung cancer for heavy smokers provides a good reference value. The relative risk of lung cancer for heavy smokers (40 cigarettes/day) is 1000% to 2000% higher than the risk for non-smokers. “Environmental” exposures that are associated with an increase in breast cancer risk are much smaller. Using our alcohol consumption example, a study which pooled the data from six large, well-designed studies (including 322,647 women, 4335 with breast cancer) reported a 40% increase in breast cancer risk among women who had between 2 and 5 drinks a day. Alcohol consumption also provides a good example of the interactive nature of exposures. Several recent studies have reported significantly increased breast cancer risk among women who consume alcohol and also have a diet low in the B vitamin folic acid.

**Dose Relationship for the Association**

In most cases, the effect of a toxic agent increases with the dose or level of exposure; the causal criteria state that evidence for a dose relationship should exist. Most epidemiological studies divide the women studied into groups depending on their level of exposure. The level of risk is frequently calculated by comparing the risk of women with no or least exposure with those who had the highest exposure. However, examinations also evaluate trends of increased or decreased risk accompanying changes in exposure. The presence of such a trend or dose relationship provides good evidence for the validity of the finding.

There is a well-established dose relationship between alcohol consumption and breast cancer risk. Several studies have found that breast can-





cer risk increases with the amount of alcohol a woman consumes each day. In the pooled data study described above, breast cancer risk increased 9% for each 10 grams of alcohol (about 1 drink) a woman consumed each day. Accordingly, women who consumed 4 drinks per day would be expected to have 40% higher breast cancer risk than women who did not drink.

### Plausibility of the Association

This criterion states that if there is a cause-and-effect relationship between a toxic exposure and risk of disease there should be supporting evidence from studies of the effects of the toxic substance in cells, animals and humans. In other words, the effects should make biological sense.

For the association of alcohol consumption and breast cancer risk there is a large amount of supporting biological evidence that the association makes biological sense. Alcohol affects breast cancer risk factors (mammographic density and estrogen levels), mammary tumor formation in animals, dietary factors which are thought to be cancer preventive, and various changes at the cellular level. Each of these effects support the linkage to cancer formation.

### Time of Exposure for the Association

This criterion is built around the idea that disease processes have a latency period, a period of time between beginning of the disease process by the toxic exposure and the appearance of the disease itself. An exposure which has a cause-and-effect relationship with a disease should occur at a time which agrees with the time period needed for formation of the disease. A latency period is especially important for breast cancer where the time period for disease formation is measured in decades. For example, a recent exposure is unlikely to be associated with the formation of cancer and would be viewed with skepticism.

The evidence for meeting this criterion for alcohol consumption and breast cancer risk is less strong than that for the other criteria. A number of studies have addressed this issue by examining if there are certain ages where alcohol consumption leads to the largest increases in breast cancer risk. Almost equal numbers of studies have found no period of highest risk as have found drinking at ages less than 25 or 30 to be linked to higher risk. Interpretation of this



evidence is complex since there are studies that suggest that alcohol may act at more than one stage of the cancer formation process. It could act at an early or an intermediate time point.

The criteria for causality define the experimental results needed to conclude that there is a cause-and-effect relationship, but knowledgeable judgment is also required for this evaluation. This is because the body of scientific evidence on almost any issue is usually incomplete as well as flawed.

Scientific studies do not proceed in a highly systematic manner with these standards being examined one by one. Rather, the forces that guide what studies are conducted are based on a number of factors including the availability of funding, the number of investigators with expertise to conduct the studies, the access to subjects for study, and the likelihood of a significant finding. These forces produce a body of evidence that may be very strong for some of the criteria and weak or nonexistent for others. Accordingly, evaluations must be made by examining the strength of the total body of evidence and the degree to which it meets the standards that would be result if a cause-and-effect relationship existed.

### Conclusion

In conclusion, a determination of cause-and-effect relationships requires a substantial body of evidence as well as knowledgeable evaluation of this evidence. Individual studies comprise small pieces of the large body of evidence needed and the answers to these complex questions are arrived at only after a great deal of study and many trials and errors. It is our hope that this article will give you the tools to see the forest—evidence needed for cause-and-effect relationships—rather than the many trees—results of individual studies of risk associations—for the various risk associations that are reported in the popular press.

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