# 2. Cause and Effect vs. Risk Factors

*Risk estimates are even more important in evaluating screening and preventive care, since individuals are counseled to seek these services. For this counsel to be ethical, not only must the action not be harmful, but it must have a reasonable chance of benefiting the person.*

Lester B. Lave[1]

Alice went to see her doctor for her annual physical. Noting that Alice was now in her forties, her doctor recommended that she get a mammogram. But Alice said she wasn't sure she wanted to do that. She had read that some experts questioned whether the benefits of the procedure were worth the inconvenience, discomfort, costs, and potential adverse effects from intervention, like radiation or biopsies. Before making a decision, she wanted more information. Only in the best of all possible worlds would Alice's doctor take the time to discuss all of these issues fully, but let's assume she did.

She told Alice that a mammogram is only a screening test designed to detect abnormalities – lumps – in the breast. She explained that if a lump were found, further testing might be necessary to see if it correlated to breast cancer. The presence of a lump would not mean that she had breast cancer, just that additional procedures might be required. In other words, there is no cause and effect relationship because the presence of a lump in the breast is not *always* associated with cancer.

Seeing that Alice was listening intently, this exemplary doctor continued.

## Cause and Effect

The doctor explained that when there are two events, with the first consistently resulting in the second, scientists recognize them as cause and effect. The cause makes something happen. The effect is what happens. She gave Alice some medical examples:

- HIV is the cause, AIDS is the effect.
- The polio virus is the cause, poliomyelitis is the effect.
- A type of parasite called a plasmodium is the cause, malaria is the effect.

In these instances, medical science has demonstrated with a high degree of certainty that a disease will occur if the agent known to be causative is present. *By definition of cause and effect, the disease-causing agent must always be present if the effect is to occur.* When a specific cause is consistently linked with a specific effect, there's little uncertainty about the diagnosis, and intervention is almost always warranted.

A number of cause and effect relationships have been confirmed. The presence of adequate levels of certain environmental contaminants (like asbestos) or specific infectious agents (such as bacteria or viruses) has been directly linked to specific diseases or health effects. Unfortunately, that's not the case with many chronic conditions, including cancer.

Establishing causality for cancer is problematic because cancer doesn't appear immediately after exposure to a cancer-causing substance. It seems to require a latency period, and this delay makes it harder – and often simply impossible – to figure out what caused it.

One typical determinant for causality is exposure to an environmental insult, like a carcinogen. As exposure to the carcinogen increases, the incidence of the disease usually increases as well. But if we can't quantify exposure, it is difficult to determine the relationship between exposure and disease with any degree of accuracy. We often find ourselves in this situation when dealing with environmental exposures because relevant levels of contaminants are very low. In most cases, is it virtually impossible to determine the time and degree of initial and subsequent exposures.

Scientists are more likely to conclude that a particular agent causes a particular form of cancer if it can be demonstrated in epidemiological studies, which are large, controlled studies of people. But with a few exceptions – asbestos exposure causing mesothelioma or radon exposure causing lung cancer in miners, for example – we have not yet been able to correlate exposure to potential carcinogens with specific types of cancer. Without multiple studies showing consistent results that verify causality, uncertainty remains. Animal experiments are another commonly used approach for determining whether or not exposure to a substance will result in cancer. Results from these experiments are used in mathematical models to predict the level of exposure which might cause cancer in humans, but they often rely on unverified, controversial assumptions that leave us with a high level of uncertainty.

## Risk Factors

If a direct cause and effect relationship cannot be demonstrated between a disease and an agent or substance that is present, yet there seems to be a statistical association between the two, the agent suspected of being asso- ciated with an effect is called a *risk factor*. In other words, *a risk factor is a biological condition, substance, or behavior that has an association with but has not been proven to cause an event or disease.*

With health problems like coronary heart disease, cancer, stroke, and diabetes – which typically have long latency periods and no documented causative agent – the medical community uses a risk factor approach to determine intervention strategies. Yet there is considerable inherent uncer- tainty when risk factors and risk analysis are part of the equation. Due to this uncertainty, we should avoid equating "risk factor" and "cause." They're simply not the same. Consider these examples: elevated choles- terol is termed a risk factor but not the cause of coronary heart disease; a lump detected in breast tissue is a risk factor but not the cause of breast cancer; childhood obesity is a risk factor but not the cause of diabetes. This distinction is critically important, since it can be very difficult to prove a statistically significant relationship between a risk factor and an effect.

Identifying a risk factor is valuable only to the extent that it can be used to predict an increased frequency or probability that a particular event or disease will occur. So when Alice was told that a lump would be classified a risk factor, it meant that a lump in the breast may or may not be associated with cancer. Her doctor explained that lumps are not necessarily cancerous.

It was becoming clear to Alice that asking the right questions and being able to interpret the answers was going to be essential if she was going to make an informed decision about having a mammogram. She needed to know:

- How strong is the association between the presence of a lump and cancer?
- Can that association be used to predict an increased frequency or probability of breast cancer?
- What is the uncertainty in the studies that have been conducted?
- Are the benefits of a mammogram worth the time, money, and potential negative impacts from intervention?
- What about the risks associated with radiation from mammograms?
- Why are risks characterized by some as significant and by others as trivial?

Ordinarily, people don't ask questions like these. But they should, since the answers leave room for people to reach different conclusions, based on how they feel about taking risks. Understanding uncertainty and the way health risks are presented is critical to making an informed decision.

Alice was fortunate that her doctor believed in the patient's right to be part of the decision-making process, understood risk analysis, and was willing to take the time to explain the basic concepts and answer all her questions. The physician proceeded to explain that the widespread use of mammograms is designed to reduce the risks and, therefore, the death rates from cancer. But, she continued, there is a great deal of controversy surrounding the benefits of mammograms. In fact, a well documented report published in the year 2000 by two Danish scientists questioned the

appropriateness of conducting this screening test without first identifying the actual benefits and predicted risks.[2]

The public hears about health benefits and risks from many sources, and there are a number of different ways to talk about their significance. While all of these approaches may be scientifically legitimate, the misinterpretation of some of the statistical relationships involved can lead to inappropriate medical intervention.

Alice wasn't a scientist, and she knew virtually nothing about statistics. Was the subject about to get too technical for her to follow? Her doctor's encouragement at this point makes sense for everyone:

*It may get a little complicated, but in a relatively short time you will be able to master what you need to know to make an informed decision. Given the importance of this matter, it's worth the effort.*

## Absolute Risk versus Relative Risk

As Alice's doctor told her, if you understand the concepts of relative risk and absolute risk, and nothing else, you'll be amazed at your newfound ability to interpret newspaper articles and TV reports on drug and diet benefits, risks, and the value of screening tests like mammograms.

Absolute risk is *your* risk of developing a disease over a specified period of time. Absolute risk is generally calculated for chronic diseases and can be expressed in different ways. For example, if it has been determined that 1 person in a 100 will get a disease, this can be expressed as a 1% absolute risk, a 0.01 absolute risk, or a 1 in 100 absolute risk.

*Absolute risk reduction* (ARR) is the difference between the absolute risks in two groups. One way of expressing the ARR is as a percentage death rate. For example, ARR could refer to differences in breast cancer death rates between two groups of women: those who get and those who don't get mammograms over a period of time (typically in the range of five to fifteen years).

Unfortunately, *absolute* risk and ARR values are rarely provided to the public. Instead, when we hear about health risks or risk reduction, we're actually hearing *relative* numbers. *Relative risk reduction* (RRR) uses the

ratio of two absolute risk numbers to measure how much the risk is reduced in one group compared to another group. With RRR numbers, the absolute risk levels for the two groups are not communicated. This is a serious problem, because relative and absolute numbers can give very different impressions, and you must have absolute risk information in order to make an informed decision.

Calculating relative risks and the relative risk reduction (RRR) is a valid statistical method, but it tends to distort the benefits to individuals when it is used to explain health risks. The real benefit is usually much smaller than it may appear. The benefits of screening tests, including mammograms, are almost always presented in relative terms. The RRR approach may be helpful to scientists and public health officials, but patients are not really among the beneficiaries. Since RRR is used by drug companies, the media, physicians, and others to characterize health risks, it's important to understand how it differs from *absolute* risk. Hopefully, the following hypothetical examples will make this clear.

## A Hypothetical 5-Year Diabetes Drug Study

- A hypothetical study investigated the effectiveness of a drug in reducing deaths from complications due to the onset of diabetes. The study group consisted of twenty thousand men, all of whom had diabetes.
- Ten thousand men were given the drug and the other ten thousand were given a placebo. The study went on for five years.
- By the end of the 5-year study, one individual in the experimental group (given the drug) had died of diabetes. In the control (placebo) group, two individuals died of diabetes.
- The absolute risk reduction (ARR), in terms of the percentage death rate, is the difference in death rates for the two groups. For the group given the drug, the death rate was 0.01% (because 1/10,000 = 0.01%). For the control group, it was 2/10,000 (because 2/10,000 = 0.02%). When you subtract 0.01% from 0.02%, the answer is 0.01%. So the ARR is 0.01%.

- Another way to look at these results is to say that of 10,000 diabetics in a room, only one would benefit from receiving this drug over a 5-year period.

Unlike absolute risks, relative risks and RRR are, by far, the most common and widely used methods for characterizing health risks. These are the values you hear and see in the media. In this example of a diabetes drug study, this would mean comparing the number of individuals who died in each of the two groups. To calculate relative risk reduction you would compare the 2 in 2/10,000 and the 1 in 1/10,000. The reduction is from 2 to 1; there is one fewer death in the group receiving the drug. Since this difference of 1 death is 50% of the 2 deaths observed in the control group, *the relative risk reduction or RRR is 50%.*

Same study. Same actual results. Expressed as 0.01% ARR or as 50% RRR. Quite a difference! Being told that taking a drug will halve your chance of dying sounds much better than being told that taking a drug would change the death rate by 0.01%, or that one person out of 10,000 would benefit over a 5-year period!

To make her point about the problem even clearer, Alice's doctor posed a variation on this hypothetical case. What if the drug was used to treat a rare disease rather than diabetes? Assume the death rate without the drug is 2 out of 1,000,000 and with the drug is 1 out of 1,000,000. *The absolute percentage rate difference is now 0.0001%, but the relative risk reduction is still 50%.* The calculation of this RRR is statistically valid, but the chance of benefiting from the drug is literally one in a million!

## The Number Needed to Treat

Alice understood everything so far and was ready for the next technical term: *the number needed to treat* (NNT). This term is used frequently in the medical literature and refers to the number of people who need to be treated in order for one person to benefit.

Let's suppose that 4 out of 100 people will normally become victims of a particular disease. A pharmaceutical company reports that a new drug reduces the relative risk of getting the disease by 25%. This means that of

the original 4 victims, one will be spared if all 100 take the new drug (25% of 4 = 1).

Here is another way to look at the situation: on average, in a group of 100 people who don't take the drug, 4 will get the disease. In a group of 100 people who do take the drug, only 3 people will get the disease. *Therefore, 100 people need to take the treatment for 1 person to benefit. The NNT is 100.*

## How to Characterize Risks

After hearing these examples, Alice wanted to apply her new knowledge and determine if mammograms would be appropriate for her. She still wanted advice and guidance from her physician, but she now realized that she would need to make the final decision based on her own perception of acceptable risk. Her doctor cautioned that before making this decision she needed to learn more about uncertainty and the different ways to characterize, or define, risks. The lesson continued.

Let's say a man reads a report from one of the major wire services in his local newspaper indicating that a new drug reduces the risk of getting heart disease by 50%. Since his father had heart disease as a relatively young man and he is overweight, he's tempted to buy and take these pills. His wife suggests he investigate the claims of risk reduction a little more closely.

The study group consisted of 1,000 men who received the drug and another 1,000 men who didn't receive any treatment. In the group receiving the treatment, two individuals were diagnosed with heart disease during the eight-year study. In the control group, four individuals got heart disease. This represented a 50% RRR (2 is 50% of 4; compare the treated group to the control group) and a 0.2% ARR (4/1,000 = an absolute risk of 0.4%; 2/1,000 = 0.2%; 0.4% minus 0.2% = 0.2%). As is often the case, the drug company only advertised the RRR of 50%. According to the study, there were also a number of serious side effects associated with taking the drug that included possible liver damage, muscular problems, and impotence.

He can't find any written information presenting the risks and benefits in a meaningful way that would help him make his decision. He realizes that the payments for this drug will be a burden. What should he do?

He decides to ignore the RRR value and focus on absolute risks instead. With his doctor's help, he finds out that there is a 3 in 1,000 chance of developing serious side effects (which are often termed "contraindications" on prescription labels). Therefore, while the risk of getting heart disease would be decreased to 0.2%, the risk of serious complications would be 0.3%. A heart attack could be fatal. The side effects would be less likely to be fatal. He also has to factor in the prohibitively high cost of the drug. It's a tough decision, but at least he has a factual basis for making an informed choice. When patients understand the real potential benefits of a drug or a procedure, they may be better able to decide if it is appropriate to forgo a treatment that may not only be expensive but also have unwanted or dangerous side effects.

Returning to the subject of Alice's mammogram, her doctor referred back to the Danish study in 2000. Its authors found essentially no meaningful decrease in breast cancer deaths in Sweden, where mammograms to screen women for breast cancer had been recommended since 1985. Furthermore, their article stated that "screening for breast cancer with mammography is unjustified."[2]

This statement was based on results from 129,750 women who had mammograms in the late 1970s and early 1980s and a comparison group of 117,260 women who did not have mammograms. Death rates from breast cancer were calculated over a twelve-year period. The death rate for the group that had mammograms was 0.4% (511 died of breast cancer) and for the control group, 0.5% (584 breast cancer deaths). The ARR is the difference between 0.5% and 0.4%, or 0.1%. This meant that 1,000 women would have to get mammograms biennially for twelve years in order to prevent one single death from breast cancer. It was on this basis that the authors recommended that mammography screening was not justified.[2]

In light of this information, Alice wanted to know why mammograms are routinely recommended to millions of women every year. Her physician explained that there have been numerous articles in the last five years on both sides of the issue, some agreeing with the Danish scientists and

others refuting their findings. Many scientists questioned bias in the studies selected for their analysis, and others questioned the experimental design of the analysis itself. On the other hand, equally prominent scientists have fully concurred with the finding that mammograms are not warranted.

Much of the controversy centered on the characterization of risk. Alice's physician asked her to use her new knowledge to calculate the RRR, using data reported in the study. Alice had learned her lesson well. She said that the difference between 0.5% and 0.4% was 0.1%; and that 0.1 was 20% of 0.5. Therefore, the RRR demonstrated a 20% relative death benefit among women who have had mammograms. The difference between a 20% RRR and a 0.1% ARR sounded dramatic, even though both numbers described the same information.

Using exactly the same data set, Fig. 2.1 demonstrates the rather striking differences in characterizing risk when using RRR and ARR. Using RRR, patients would be told that women who have biennial mammograms are 20% less likely to die of breast cancer. Using ARR, a patient would learn that there is a 0.1% reduction in the breast cancer death rate for women who have biennial mammograms, and that the NNT is 1,000. When event rates are low, ARR becomes smaller. RRR often remains constant. This is yet another reason to question the value of relative risks.

Her doctor then cited another case, which involved the characterization of risks and benefits from taking the drug tamoxifen. News headlines like "Tamoxifen Cuts Breast Cancer Risk by 50% in Healthy Women!" were proclaiming the drug. Of course, the media reported the RRR. In the actual medical study, less than 2% of women taking tamoxifen got breast cancer, and less than 3% of those taking the placebo got breast cancer. The absolute rate difference was about 1%.[3]

Alice now understood how important it was to know the absolute risk values when making a decision based on risk analysis. But she wondered if there were other factors to consider on the risk side of the equation. What about radiation risks, or risks from associated procedures like biopsies? What about the uncertainty in the large studies that served as the basis for the characterization of risk?

## A. Absolute Risk Reduction
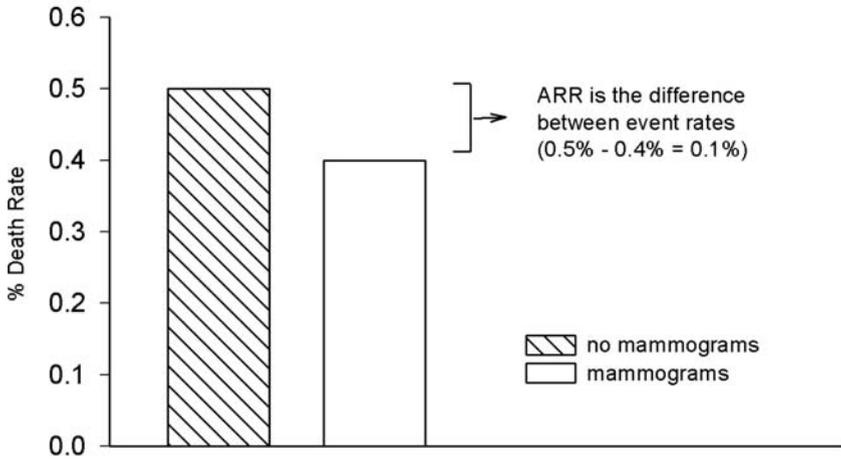


## B. Relative Risk Reduction
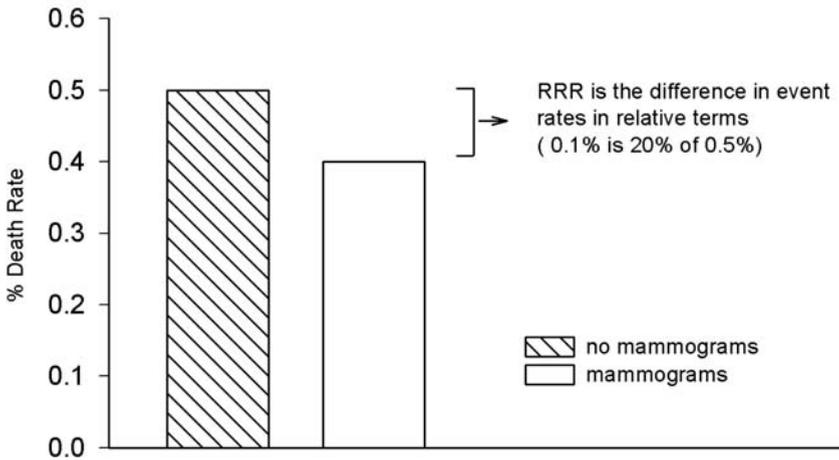


**Fig. 2.1.** The bars in both graphs represent the percent death rate for women in Swedish mammography trials. It is obvious that graphs A and B represent the same data, which are used to calculate both absolute risk reduction and relative risk reduction. **A.** Absolute Risk Reduction (ARR) is 0.1%, **B.** Relative Risk Reduction (RRR) is 20%

Alice's doctor told her that her questions were well-founded, but that she was not aware of any report combining all of these factors to determine overall risks from mammograms.

Radiation from repeated mammograms is a real concern. Although dosage levels have been reduced thanks to modern equipment, screening at an early age and frequent examinations would increase radiation dosage and, perhaps, the chance of cancer. Whether that increased chance would meaningfully impact the ARR is unclear.

Her doctor then addressed Alice's question on associated and potentially unnecessary procedures. Doctors will order a number of "additional tests" for every 10,000 mammograms given to healthy women. These include 358 breast examinations by ultrasound, 104 "aspiration" biopsies (where fluid and cells from the area of the breast with the abnormality are removed), and 209 surgical biopsies (removal of part of the breast containing the abnormality). As it turns out, the majority of the "abnormal" mammograms will prove to be false positives, and only about 25 of the women will have breast cancer.[4] The bottom line was that the risks from these procedures didn't seem to be reflected in the ARR either.

The doctor thought that Alice's point about uncertainty in the large epidemiological studies of hundreds of thousands of women was a very important one and merited some additional discussion. While it is generally agreed that there is less uncertainty when studies involve people rather than animals, there are still many areas that can be problematic. Were there enough people in the control and experimental groups? Was the analysis conducted in a rigorous manner? Was there an appropriate statistical evaluation of the data? Was there a description of the statistical methods used? Was bias identified and addressed properly? And so forth.

The design of the study, how it is conducted, how the results are interpreted – these are all areas of potential uncertainty. Without a description and explanation of this uncertainty, it's difficult to characterize absolute risks accurately.

Risk characterization is designed to bridge the gaps between doing a risk assessment, choosing risk control options such as medical intervention, and determining acceptable risk, i.e., risk management. Theoretically, risk characterization describes the risks both to individuals and to populations,

communicates the results of the risk assessment, develops clear and implicit statements of strengths and weaknesses, and evaluates the overall quality of the assessment. In characterizing health risks, care must be taken not to trivialize or exaggerate risks. Perhaps most important, the objective characterization of risk requires that numerical estimates never be separated from the descriptive information about uncertainty, because numbers tend to take on a life of their own.

We want to believe that diagnostic tests *must* be beneficial. But this view does not always properly weigh the merits of a test against other factors, such as side effects and the consequences of false positive results. Deciding what level of risk is acceptable should involve a value judgment on the part of the patient.

Alice now understood what she really needed to make an informed decision, so she asked her doctor for objective, written information including charts, which would compare individual and population risks and discuss absolute risks, absolute risk reduction, decreased life expectancy, risks from intervention, uncertainty, and overall benefits from mammography. Apologetically, the doctor said she didn't know where to locate that information and doubted whether it could be found in any one place. It was clear to both Alice and her doctor that it would be extremely helpful if health risk assessments – including a full and open discussion of uncertainty – were made transparent to the public. Such information would lead to more appropriate use of screening tests and a greater understanding of drug benefits and side effects.

Alice decided to postpone any decision on having a mammogram until she could track down, review, and interpret all the relevant information. Her doctor agreed.

## Summary

It has been estimated that 30 million mammograms are done in the US each year. During the past five years, there have been dozens of articles in reputable, peer-reviewed medical journals addressing the central question: is screening for breast cancer with mammograms justifiable? There are

many different views on the subject, but one thing is clear – it is a controversial issue.

It is likely that a large percentage of women will be satisfied to take the recommendation of their physicians and continue to have annual or biennial mammograms. It is also reasonable to assume that many women would want to know more about the risks and benefits of mammography before making a decision about having the test. Unfortunately, at present patients are not given the information they need to make an informed choice. And in most cases they don't even know what they're missing. Risks and benefits associated with screening tests and medical intervention in general are almost always characterized in terms of RRR. As a result, reports in the popular media, medical literature, and pharmaceutical advertisements often make the benefits seem far more impressive than they really are.

*While RRR is a useful yardstick for research scientists, it should not be used by the public to assess the risks and benefits of screening tests. Far more weight should be given to ARR values.*

ARR is the simple difference between event rates, such as death rates. If the reduction in absolute risk is communicated, patients can easily determine the number of individuals who would have to be screened for one person to benefit, known as the number needed to treat (NNT). This may well be the most meaningful reference point for patients interested in being involved in the decision-making process. RRR values do not provide any insight into this very important measure of risk.

In the case of mammograms, the absolute risk reduction is 0.1%, which means that the NNT is 1,000. Using ARR, patients would be told that there is a 0.1% reduction in deaths among women who have biennial mammograms when compared to those who have not had biennial mammograms. Therefore, 1,000 mammograms would have to be given in order for one person to benefit.

Additional information on other risks from intervention, including biopsies, radiation, false positives, and false negatives should also be provided to women who are facing a decision on whether or not to have mammograms. A woman would then be in position to consider all the risks and weigh the odds that she would be the one individual in 1,000 to benefit

from biennial mammograms. Would she make the same decision if the NNT were 100,000? What if it were 10? The decision would be personal, and it would depend on how risk-averse that woman was. What's right for one woman might not be right for another.

In light of this situation, the medical community should provide women with an accurate assessment of the harm and benefits from screening mammography, even if this means acknowledging the overall uncertainty in assessing this health risk. Different individuals may well prefer different options when it comes to choosing a treatment based on a risk assessment.

Given the large numbers of women who might welcome and benefit from this kind of educational material, it is difficult to understand why it is not already being provided routinely. Whatever the reason, it leaves women today with two choices: go along with the status quo, or demand objective information from their doctors regarding the risks, benefits, and uncertainty associated with mammograms.