AN INTRODUCTION TO EVIDENCE-BASED CLINICAL PRACTICE: 2. A CONCEPTUAL APPROACH TO CAUSATION: PART 1

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One of the most common questions that arise in clinical practice is whether a causal relationship exists between two factors. Does a medicine *cause* an improvement in the symptoms of a patient? Does an exposure to a substance *cause* the development of disease? Determining whether causal relationships exist is a multi-step process. It begins first with determining if an association exists between two factors, then determining if the association is a consequence of error and finally identifying further evidence to support the fact that the association represents a cause and effect relationship. We will take the reader through these series of steps as a CAM provider is confronted with the question of whether silicone breast implants cause the development of arthritis.

Figure 1: Three Questions Needed to determine causality
1. Is there an association between treatment / exposure and effect ? **2. Can this association be due to error (either bias or chance)?** **3. Is there other evidence to support a cause-effect relationship ?**

Clinical Scenario

A 45 year old women presents to a CAM provider with complaints of sore ankles and wrists. She has been reading on the internet how silicone breast implants have been implicated in the development of arthritic conditions and reveals to the CAM provider that she had implants 10 years ago. This is the third patient with silicone implants who has presented to the CAM provider with these symptoms. Our CAM provider also remembers recently reading an article in the newspaper which reported a study stating that 35 of 125 women (30%) who had silicone implants later developed rheumatic complaints which included symptoms of arthritis (1). She asks herself the question: Do silicone breast implants cause the development of arthritis?

I. Determining if an association exists

The first step in our CAM provider's attempt to identify if a causal relationship exists between two factors is to find evidence of an association. She has to determine if her clinical experience or the newspaper article she read provides adequate information to determine if an association exists between the presence of silicone implants and the subsequent development of arthritis. One way our CAM provider can answer this question is to summarize the information she has in a 2 X2 table. The use of this quick and easy method allows her to visually assess whether or not an association between silicone implants and arthritis has been demonstrated in the study.

		Outcome	
		Development of Arthritis	
		+	**-**
Exposure: Silicone implants	+	A	B
	-	C	D

Using this table she recognizes that most of her clinical decisions are based on evidence summarized either by Block A (individuals exposed to silicone implants who develop arthritis) or Block A and B alone (individuals exposed to silicone implants who develop arthritis versus exposed individuals who do not develop arthritis). An example of decision-making based solely on block A would be our CAM provider relying on her clinical experience of 3 individuals who received implants and who subsequently developed arthritis symptoms. An example of decision-making based on only Blocks A and B would be basing her decision on the newspaper report of 120 individuals with silicone implants, 35 of whom developed rheumatic symptoms. Our CAM

provider realizes that, in order to determine if an association exists between exposure to silicone implants and development of an inflammatory arthritis, she will need information from all four boxes. Specifically, she will need to know the following: in all those exposed to silicone implants how many individuals have developed arthritis and how many have not (Blocks A and B), and in all those *not* exposed to silicone implants how many individuals have developed arthritis and how many have not (Blocks C and D).

Recognizing the limitations of her existing information, specifically, the lack of a *control population*, our CAM provider conducts a search of the literature and identifies a study she feels is appropriate to answer the question of whether silicone implants are associated with the development of arthritis. This study, by Giltay et al. evaluated the association of breast implants with a variety of symptoms which included joint pains (2). The study identified 235 women whom had received silicone implants and an age matched control group of 210 women who had received another form of plastic surgery. The investigators mailed questionnaires to patients and controls inquiring about a variety of rheumatic symptoms, including the presence of joint pain lasting three months. The results of the study can be summarized in the following two by two table:

		Outcome		
		Development of joint pain		
		+	**-**	**Total**
Exposure: Silicone implants	+	46	189	235
	-	18	192	210

Our CAM provider determines that, according to this information, individuals who were exposed to silicone implants had a rate of developing joint pain of 20%([46/235] *100) while those who were not exposed to silicone implants had a rate of 9% ([18/210]*100). Thus women

with silicone implants were approximately twice as likely (20%/ 9% = 2.3) to develop joint pain than those without implants. Base on this study, it appears as if an association exists between silicone breast implants and joint pains. However our CAM provider must go through several more steps to determine if a causal relation exists.

II. Determining the nature of the association

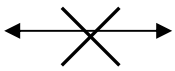
Our CAM provider must next determine the nature of the association observed in the study. Four distinct possibilities exist to explain the association she observed:

(1) The observed association is a consequence of chance or bias

(2) Silicone breast implants cause arthritis

(3) Arthritis caused the patient to be obtain silicone breast implants

(4) Silicone breast implants and the development of arthritis are both related to a third factor (for e.g. women with implants belong to a demographic group that is at higher risk of developing arthritis).

(1) Silicone Implants  Development of arthritis symptoms

chance/bias

causal

(2) Silicone implants ⟶ development of arthritis symptoms

causal

(3) development of arthritis symptoms ⟶ exposure to silicone implants

(4) development of arthritis symptoms exposure to silicone implants

third factor

In order to sort through these four possibilities our CAM provider wants to examine the study for sources of error and then look for supporting evidence of a causal relationship. She recognizes that the results of the study she has reviewed are susceptible to two forms of error; systematic and unsystematic. Systematic error is also known as bias and refers to a third factor that consistently distorts the relationship between the two factors of interest towards one direction. Unsystematic error refers to the likelihood that the results of the study occurred by chance.

a. Systematic error or Bias

Our CAM provider recognizes that bias can occur at two points in the conducting of a study: the *selection of* and the *measurement of study results*. Selection bias occurs when patients in one group (either the exposed group or the control) are systematically different from those in the other group. This systematic difference introduces the potential for confounding – the presence of a third variable related to both the exposure and the result that alters the association between the two. For example, as the study relied upon response to a survey, the potential exists for patients with silicone implants who chose to not respond to be healthier (and less likely to have arthritis) than patients in the control group who didn't respond. This would increase the likelihood of observing an association when one does not exist. Measurement bias occurs when the observations of outcomes in one group are systematically different from observations in the

other group. For example, the patients who have received silicone implants may be more aware of development of symptoms than the controls due to the media attention concerning potential adverse effects of the implants

The primary mechanism by which systematic error is controlled for is through the study design. Several different study designs are used to determine if an association exists between two variables. These are summarized in Table 1. The strongest study design for identifying a causal association is the well designed randomized controlled trial. This form of study reduces selection bias by randomly allocating patients to either exposure or control. Randomization maximizes the likelihood of the equal distribution of known and unknown confounders between the two groups. A confounder is a variable that is associated with both the exposure and the outcome that distorts the relationship between the two. For instance, epidemiological studies have determined an association between cigarette smoking and liver cirrhosis (3). However, this was likely not a direct effect of smoking but rather the fact that smokers were more likely to be significant consumers of alcohol. Thus alcohol was an important confounding variable.

Often randomized controlled trials cannot be conducted due to cost, logistical or ethical issues and observational studies have to be relied upon. The observational study with the highest level of validity is a well-designed controlled prospective cohort study. In this study two groups of individuals are followed prospectively. Of these two groups, one will be exposed to the agent of interest and the other will not. Outcomes in both groups can then be compared. When the outcome of interest is rare or the latency period between exposure and outcome is long, a case-control design is often utilized. In this design a group of individuals with the condition of interest (e.g. arthritis) is identified, as is a control group. The rates of exposure to the risk factor of interest (e.g. silicone implants) can then be compared between the two groups. As efficiency is improved with each of these study designs, the potential for bias also increases.

Our CAM provider reviews the methods in the study and determines that it is a form of retrospective cohort study. Individuals and controls were identified at the incident time of

exposure (silicone implants, control surgery) and monitored to determine development of symptoms. This was done retrospectively via a questionnaire. She recognizes that this form of study is susceptible to both selection and measurement bias.

b. Unsystematic error or chance

Our CAM provider next checks for the potential for unsystematic error – an inaccurate association due to chance. The likelihood of this type of error occurring in a study can be identified through statistical tests. In reviewing the results of the study our CAM provider finds a statistic that states the likelihood of the results occurring by chance are less than 1 percent (p value <0.01). In determining if this level of association is of adequate strength she weighs two factors: what are the potential benefits of an exposure and what are the potential harms caused by the exposure. She believes that the development of arthritis is an important outcome which can impact on the quality of life of her patient. While silicone implants may have a cosmetic importance to her patients there are other options available. She is willing to accept up to a 10% chance that the results of the study occurred by chance, well above the less than 1% chance observed.

Summary

Our CAM provider was confronted with the question of whether silicone breast implants cause the development of symptoms of arthritis. In addressing this question she first identified a study with a control group so that she could determine whether an association existed. This study demonstrated a 2.3 times increased risk of symptoms of arthritis in women with silicone implants compared to controls. She next examined the study for sources of error. She identified the potential for systematic error in both the selection of patients and measurement of effect.

However, she found that the likelihood of the observed association occurring due to unsystematic error (chance) was remote. Based on the information provided our CAM provider is not completely confident of a causal relationship. She recognizes she needs additional supporting information. In the next article in this series we will describe additional criteria which helps establish a causal relationship.

Table 1 **DIFFERENT STUDY DESIGNS FOR ESTABLISHING CAUSATION (IN APPROXIMATE ORDER OF VALIDITY)**

Randomized trial	an experimental study in which allocation of patients to intervention or control occurs by chance.
Cohort study	a form of observational study in which a group of individuals exposed to the variable of interest and a group of unexposed individuals (controls) are followed prospectively to determine rates of developing the outcome of interest.
Case-control study	a form of observational study in which a group of individuals with the outcome of interest and a group of matched controls are identified. Both populations are then retrospectively studied to determine exposure to the variable of interest.
Ecological study	in this form of study exposure to a risk factor and development of an outcome are characterized by the average exposure to the risk factor and development of the outcome in the group to which individuals belong (e.g. increased wine consumption in France and reduced cardiovascular mortality).
Case series	this form of study involves identifying a group of individuals with the outcome of interest and describing their characteristics and clinical course.
Case study	the description of a single patient with the outcome of interest

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