Disease Versus Etiology: The Distinction Should Not Be Lost in the Analysis

The relationship between bone mineral content (BMC) and fracture has been approached in the medical literature from two distinctly different perspectives. The first approach employs the methodology for evaluation of diagnostic tests; the usefulness of the test is described by its sensitivity and specificity. The second approach models the probability of fracture as a function of BMC, and employs the methodology usually used for characterization of disease risk factors. When the same data are analyzed by these two approaches, the results and conclusions will differ. Thus the choice between these two approaches is not trivial; diagnostic tests and risk factors are inherently different, and require different analytic approaches.

A diagnostic test detects the presence (or absence) of disease. A radiograph for a fracture, an imaging technique for a tumor, or a biochemical marker released from damaged tissue might all serve as diagnostic tests. A risk factor, on the other hand, is a cause of disease, or a variable associated with a cause of disease, although the term risk indicator may be more appropriate in the latter situation (*1*). Smoking, alcohol, and exposure to infectious agents or toxins are known risk factors for disease. Anatomic or physiologic variables can also be risk factors. Examples include cholesterol, obesity, blood pressure, and bone mass; the latter two might also be considered risk indicators. One disease can also be a risk factor for another; an example is diabetes as a risk factor for coronary artery disease (*2*).

Risk factors precede disease occurrence, while diagnostic tests detect disease after it has occurred. Risk factors may persist at the time of disease onset, such as low bone mass at the time of fracture; however, the risk factor need not coexist with the disease. For example, radiation and carcinogenic chemicals can be risk factors for cancers that appear many years after the causative exposures.

Both risk factors and diagnostic tests are used in clinical decision making. Knowing that an individual has either symptoms or risk factors for a disease makes it more likely that the person truly has the disease. Risk factors are often used to narrow the diagnostic possibilities. What pediatrician, for example, would not inquire about the possibility of ingested toxins when a child presents with a severe stomach pain? This would help differentiate chemical poisoning from a flu syndrome. Risk factors such as age, occupation, and smoking status can provide valuable diagnostic clues. Information about risk factors may point to the need for specific diagnostic tests.

For a diagnostic test, sensitivity and specificity are the defining properties. Sensitivity is the proportion of cases testing positive. Specificity is the proportion of non-cases who are negative with the diagnostic test. A useful diagnostic test has a sensitivity and specificity that remain nearly constant in different test populations. A diagnostic test that is readily affected by variations in age, sex, race, and health status would be difficult to apply in the varied realities of clinical medicine.

In contrast, the terms sensitivity and specificity have wholly different meanings when applied to risk factors. Sensitivity is nothing more than the prevalence of the risk factor among the diseased; thus the sensitivity of smoking for lung cancer would be 0.85 if 85% of the patients with lung cancer were smokers. Analogously, specificity corresponds to the prevalence of the risk factor among the nondiseased. If 35% of the people without lung cancer were smokers, the specificity would be one minus this proportion, or 0.65. The prevalence of risk factors such as blood pressure, diet, and smoking can vary widely between populations, and between the sick and the well. As a consequence, for one risk factor, sensitivity and specificity can also vary widely, as illustrated in Table 1. In this example, five hypothetic populations are illustrated. In all five populations, 96% of the people exposed to the risk factor, and 31% of the unexposed, developed disease. In contrast to a good diagnostic test, the sensitivity and specificity for the risk factor ranged from <10% to >98%. Thus the same risk factor can have high, medium, or low, sensitivity as well as specificity. For a continuous variable, such as BMC, the distribution of the risk factor in the population describes the risk

TABLE 1
Illustration of the Potential Variability of Sensitivity and Specificity for the Same Risk Factor in Different Populations*

Number of people*					
RF = + DIS = +	RF = + DIS = −	RF = − DIS = +	RF = − DIS = −	Sensitivity	Specificity
500	20	80	180	0.862	0.900
500	20	8	18	0.984	0.474
500	20	800	1,800	0.385	0.989
50	2	800	1,800	0.059	0.999
5,000	200	8	18	0.998	0.083

* Distribution of the risk factor (RF) and the disease (DIS) within the five hypothetical populations. Ninety-six percent of the people exposed to the risk factor and 31% of the unexposed developed disease in all five populations.

factor prevalence. BMC distributions are known to vary markedly between different ages, and likely vary by race, ethnicity, physical activity, diet, and other factors. Sensitivity and specificity, as measures of risk factor prevalence, will vary not only between populations, but in the same population over time. For this reason, the clinical utility of BMC measurements is poorly characterized by reports of sensitivity and specificity.

We can also compare risk factors and diagnostic tests in the clinical management of a single patient. For our patient we want to determine the probability that he or she has a disease once we know the test result. With a diagnostic test we need to know more than the test sensitivity and specificity in order to determine this probability. We need, in addition, the pre-test probability that the patient has disease. This is the basis of Bayes' Theorem: the post-test probability of disease is a function of both the pre-test probability of disease and the test result. This relationship is fundamental in relating diagnostic test results to clinical decision making.

When risk factors are used in patient diagnosis, we do not need to know sensitivity, specificity, or the pre-test probability of disease in order to determine the patient's probability of disease. The disease probability is determined from the probability associated with the presence or absence of the risk factor. For example, a worker exposed to asbestos fibers has the same risk of developing mesothelioma regardless of the prevalence of this disease, or the number of other exposed workers. His risk is the probability that his asbestos exposure would cause him to develop mesothelioma. As a further example, a woman with low BMC has the same fracture risk whether she is living in a college town or in a retirement community. Her fracture risk is unchanged by the local prevalence of low BMC or of fractures. Her fracture probability is the probability associated with her particular BMC. The defining property for BMC, as for any risk factor, is its relationship to be probability of disease. Once a risk factor is characterized, a patient's probability of disease can be determined without the use of Bayes' Theorem.

Another contrast between diagnostic tests and risk factors is evident when we consider screening. With a diagnostic test screening often refers to the detection of asymptomatic disease, as in breast cancer screening. In this case the disease is either present or absent, although various stages of disease may be determined. On the other hand, risk factor analysis offers an alternative form of screening, namely, screening to identify individuals without disease who are at high risk for developing disease in the future. Screening with risk factors might be accomplished using biographical information, such as an employment history for occupationally-related diseases. Alternatively, risk factor screening can be performed with physical tests, such as measures of blood pressure, serum cholesterol, and BMC. With either type of information we want to identify individuals likely to develop disease in the coming years. The objective is to alert us to the increased probability of disease in certain individuals. With that information, we can then either prevent the disease (if we have the means), or target those individuals for diagnostic testing for early disease detection. By identifying people

at high risk, the efficacy of intervention can be improved. So a timescale difference is also apparent: diagnostic tests are for current disease detection, whereas risk factor screening determines future disease risk.

Therefore, risk factors and diagnostic tests are inherently different, whether examined in populations, individuals, in diagnosis, or in screening. Risk factors are associated with disease causation, while diagnostic tests are used to detect disease. Because they are different, separate methodologies have been developed to analyze risk factor presence and diagnostic test results. The objective of risk factor analysis is to determine the probability of disease for different levels of the risk factor. These probabilities do not vary with the disease prevalence; they can be used directly in clinical decision making. For diagnostic tests a more indirect approach is necessary, since the probability of disease, given the diagnostic test result, is dependent upon disease prevalence, or another measure of the pre-test probability of disease. The post-test disease probability can still be calculated using Bayes' Theorem if test sensitivity, specificity, and the prevalence of disease are known. In clinical practice risk factors and diagnostic tests can provide independent contributions to diagnosis. Knowing an individual's risk factors, for instance, may alter their pre-test probability of disease and, as a consequence, influence our interpretation of diagnostic test results.

Because risk factors and diagnostic tests can both be used in clinical diagnosis, confusion sometimes arises in selecting the appropriate method of analysis. The goal in both cases is to determine the probability that a patient has the disease under consideration, but the methodologic approaches are distinct. Given the essential contrasts between risk factors and diagnostic tests it is important not to mistakenly analyze risk factors as diagnostic tests, and vice versa. While the formulas can be made to work, the results can be highly misleading.

Various examples have been used to highlight the differences between risk factors and diagnostic tests. One such example concerns the use of BMC in fracture risk management. Determining the relationship between BMC measurements and fracture risk is a complex undertaking, involving many issues beyond the scope of this article. An important first step, however, is to correctly define the problem under investigation. BMC should be viewed as a risk factor with a continuous distribution in any given population. With reduced BMC the risk of fracture increases. BMC is not a diagnostic test; the correct methodology is that of risk factor analysis (*1,3–5*). With risk factor analysis we can determine the distribution of risk in the population. In addition, we can calculate relative risks (risk ratios) and attributable risks (risk differences) to contrast the bone strength of individuals with different BMC values. We can also determine the percentage of fractures attributable to low values of BMC, e.g., the population attributable risk, that is useful in developing strategies for fracture prevention. These basic epidemiologic measures have already proven their value in defining the risk factors for heart disease, cancer, and other acute and chronic diseases.

For individual patients BMC measurements can provide a personal risk assessment. For health planning purposes BMC measurements indicate the distribution of risk within the population. However, these measurements are not intended to diagnose fractures in either situation. The objective is not to replace the radiograph in diagnosing fractures, or to determine who should receive a radiograph. The objective is to identify those at high risk of sustaining fractures. Ideally, such individuals should be identified long before any fractures occur, so that preventive action can be taken. Blood pressure and cholesterol are examples of other risk factors that identify people at high risk of disease. Decisions regarding the use and utility of blood pressure and cholesterol measurements have routinely been based upon measures of risk. The application of similar methodology to BMC measurements could help resolve some of the current controversies in this field.

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