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Commentary

When Work is Related to Disease, What Establishes Evidence for a Causal Relation?

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Establishing a causal relationship between factors at work and disease is difficult for occupational physicians and researchers. This paper seeks to provide arguments for the judgement of evidence of causality in observational studies that relate work factors to disease. I derived criteria for the judgement of evidence of causality from the following sources: the criteria list of Hill, the approach by Rothman, the methods used by International Agency for Research on Cancer (IARC), and methods used by epidemiologists. The criteria are applied to two cases of putative occupational diseases; breast cancer caused by shift work and aerotoxic syndrome. Only three of the Hill criteria can be applied to an actual study. Rothman stresses the importance of confounding and alternative explanations than the putative cause. IARC closely follows Hill, but they also incorporate other than epidemiological evidence. Applied to shift work and breast cancer, these results have found moderate evidence for a causal relationship, but applied to the aerotoxic syndrome, there is an absence of evidence of causality. There are no ready to use algorithms for judgement of evidence of causality. Criteria from different sources lead to similar results and can make a conclusion of causality more or less likely.

Key Words: Causality, Occupational medicine, Occupational diseases, Epidemiological studies

Introduction

Establishing a work-related cause of a disease is one of the most challenging aspects of occupational medicine. In practice, physicians face the challenge of making a diagnosis of occupational disease in an individual patient [1]. This constitutes a clinical diagnosis, assessment of the past exposure, and exclusion of other potential causes, which demands specialist skills in both clinical medicine and occupational hygiene. Researchers have to make causal inferences about an occupational origin from observational studies that often leave room for alternative interpretations [2]. It is therefore conceivable that these difficulties lead to undesirable variations in practice, which is often regarded as a lack of quality such has been described for reporting of occupational diseases in Europe [3].

Currently, it is generally accepted that evidence from scientific research should be used to underpin decisions about health problems to improve the quality of health care. About 20 years ago, this idea was first strongly advocated by Sackett et al. [4]. He applied the idea of what he called *evidence-based medicine* to clinical decision-making at the individual patient level. In mainstream medicine, the most important decisions are about therapy and most of evidence-based medicine has focussed on evidence to support therapeutic decision-making at the individual patient-level.

This raises the question, what establishes evidence to underpin the diagnosis of an occupational disease? Put more precisely, what constitutes evidence for the labelling of a disease as being occupational in origin? For clinical practice, I would

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expect a clinical algorithm that guides the physician in making the decision that there is an occupational cause at work in this disease, in this particular patient. However, I haven't been able to locate articles that describe such a process.

For research, I would expect a similar algorithm that would guide a researcher or a reader through the process of making a decision on work-relatedness when judging a research report on the occupational origin of a disease. Surprisingly little has been published on this topic. In this article, I will restrict myself to the assessment of causality in reports of research.

Therefore in this article, I would like to present arguments for what can be considered evidence for an occupational disease. I will elaborate the various aspects of assessing an occupational disease and the arguments for causation in observational epidemiological studies. Finally, to illustrate the process, I will apply the arguments put forward to two cases of putative occupational diseases.

Occupational Disease

Employment is associated with better health than unemployment. This positive effect of work on health is assumed to be meditated by a higher income, a purposeful social role, and a time structure for those that are employed [5]. On the other hand, workers are exposed to various kinds of health hazards at work. These health hazards may lead to occupational diseases under certain conditions. Occupational diseases can conveniently be defined as diseases that result from exposure during work activities to conditions or substances that are detrimental to health. Thus, occupational diseases can be regarded as an undesirable by-product of working. In most countries, the employer is held responsible for eliminating hazardous exposures at work. If occupational diseases still do happen, it is often regarded as a form of injustice that should be compensated financially by the employer. As part of social security systems, this professional risk is insured but there is a great variation between systems [6]. One of the aspects that varies between systems and countries in which diseases are considered occupational in origin and would need to be financially compensated. One of the main issues here is how big a part of the cause of a given disease should be assigned to occupational in origin. In legal terms, this is often defined as a higher probability of an occupational origin of the disease than of a non-occupational cause. This is then in turn translated to the criterion that more than 50% of the disease should be attributable to work.

To overcome or maybe to avoid the discussion about the amount of attribution to work, occupational diseases have been divided into 'real' occupational diseases and work-related diseases. The former are then defined as those occupational diseases that are mainly caused by factors at work such as mesothelioma. The work-related diseases are then named multi-causal or diseases in which work plays a minor role in causation such as in occupational back pain. Another way of formulating this is to say that the attributable fraction of work to occupational diseases should be substantial.

When thinking about causes of disease, it becomes quickly clear that this division is difficult to maintain, because all diseases are multi-causal. Even in the case of mesothelioma, it is not just the exposure at work but also more distant factors such as genetic make-up and social circumstances that are causes of the disease. Even without exposure to asbestos, mesothelioma does occur even though the risk of occurrence will be much less. At the individual level, it is therefore impossible to point to one cause as the main cause [7].

Another argument that has been used to distinguish work-related from occupational diseases by their attributable fraction is that the potential for prevention is bigger when the attributable fraction is bigger [1]. The preventive impact is however more dependent on the prevalence of the disease than on the attributable fraction. Preventive interventions at work that have only a small attributable fraction but that are aimed at diseases that are prevalent will prevent a larger number of persons to become ill than those interventions that have a large attributable fraction but where the disease is not very prevalent. Nevertheless, this is only a gradual difference and not a fundamental difference and does not help much in delineating work-related and occupational diseases.

This leaves us with the definition above that defines occupational diseases as any disease that results from exposure at work. There are three important elements in this definition that call for evidence; disease, exposure, and the relationship between these two.

Evidence for Disease

One of the issues that have often led to vigorous debates is what constitutes disease [8]. A disease is diagnosed by means of symptoms, signs, and other data, such as laboratory or imaging results. For some diseases, there is a gold standard, such as certain pathophysiological findings that have to be present to make the diagnosis. Then, the value of other diagnostic information can be judged with the gold standard as the point of reference. However, many diseases lack such a gold standard and thus, diagnosis becomes arbitrary and gives easily rise to debate. The debate concentrates on whether a symptom or a cluster of symptoms constitutes a disease. Repetitive Strain

Injury and Chronic Fatigue Syndrome are good examples of diseases that have been discussed in the past. The naming of a cluster of symptoms as a disease has considerable societal consequences in terms of status in society and qualifications for benefits and insurance claims.

Discussions are usually resolved by a consensus process or a Delphi-procedure that leads to a *case-definition* that is acceptable to most stakeholders [9]. A case-definition is a minimum set of symptoms, signs, and other data that are needed to establish the diagnosis. Preferably, this should be based on the diagnostic value of these characteristics related to a gold standard that is pathognomonic for the disease. However, there are few diseases that can be diagnosed based on such a gold standard and debate arises, especially when the gold standard is missing. Then, consensus is the only method to come to a joint conclusion. This does not mean that other evidence than consensus could not play a role. Sometimes, new clusters of symptoms overlap with existing ones such as was the case for repetitive strain injury, in which the case-definition included existing musculoskeletal conditions of the arm. Sluiter et al.[10] described these conditions in what they called a criteria document and that greatly facilitated the discussion on the occupational causes of repetitive strain injury. Research and practice in the area of chronic fatigue syndrome advanced when consensus was reached on a case-definition [11]. Thus, evidence for the disease component should be preferably based on symptoms, signs, or other data that have some reference to a gold standard or consensus-based case-definition.

Evidence for Exposure

In occupational medicine, we often deal with exposure in a very superficial way, because in the clinical situation or in a patient-doctor encounter, it is impossible to assess what the exact exposure would be. It is however a critical element in the assessment of the occupational origin of diseases [12]. With exposure of low-intensity and low-frequency, the risk of disease is much less than with constant exposure of high intensity. The mere existence of exposure does not necessarily imply a real health risk. The gold standard for exposure would be objective measurements of the condition or substance related to both the intensity and the duration or frequency of exposure at the individual level. In many studies and clinical situations, self-reported exposure is relied upon. Here, we would like to see evidence of the validity of the self-reported exposure in relation to objective measurements. The same holds for other estimates of exposure, such as diaries, job-title, or expert-assessments.

Evidence for a Causal Relationship

Generally in science, experiments in which the conditions are strictly controlled and the outcome can be readily observed have the biggest potential to influence our beliefs. In medicine, experiments with patients in the form of randomised controlled trials (RCTs) are regarded as the highest level of evidence. From the ethical viewpoint, a RCT can only be allowed to be performed after other laboratory and animal research has shown that a certain treatment is safe and potentially effective. The amount of evidence that a RCT altogether produces is thus bigger than only the results of the experiment. For treatment and prevention, we like to see such evidence from a produced RCT, before we would introduce an intervention into daily health care. Some argue that for preventive interventions, stronger evidence is needed than for therapy interventions because of the possibility of causing harm to healthy persons [13]. On the other hand, the absence of evidence should not always preclude preventive action. A careful balancing of benefits and harms can also lead to a so-called precautionary approach that supports action before strong evidence is collected [14].

In some cases, when the effect is big and immediate, we don't need experiments to believe that an intervention is effective. We don't need a RCT to evaluate the effect of a parachute to prevent death from jumping out of a plane [15]. Even though this example seems ridiculous, it illustrates the point well.

In many other situations where the effects are not big and immediate, it is not possible to carry out experiments. Where we suspect that a condition or a substance at work is hazardous to health, it is not ethical to carry out an experiment because one would potentially harm healthy persons. We have to rely on observational data over which we have less control than in an experiment. This makes the drawing of conclusions more difficult.

Causal inference has a long tradition in philosophy and epistemology, but it still remains difficult in practice. In our field many eminent researchers have tried to give practical guidance on how to make causal inferences based on research findings. Sir Austin Bradford Hill is one of the most well-known of these who put forward criteria for causality of a certain cause and effect. Hill had ample experience with occupational health research and the criteria list was developed as part of a lecture for the then newly established section of occupational and environmental medicine of the Royal Society of Medicine in the UK in 1965 [16]. He used similar criteria as those previously used by the US Surgeon General to make an assessment of the causal relationship between smoking and lung cancer. Hill argued that there was more reason for causal inference

if the relation between the cause and the effect was stronger, as indicated by a high relative risk. His other arguments for a causal relationship were consistency in results between studies, specific causes leading to specific effects, the cause preceding the effect, more of the cause leading to more of the effect as in a biological gradient or dose-effect relation, other biological plausible explanations for a causal effect, evidence from other sources being coherent with the epidemiological evidence, evidence from an experiment and finally analogous examples of a similar cause and effect relationship. His paper is freely available through PubMed and for a better understanding of his reasoning it is recommended to read the original text. Hill ends his list with stating that "none of these criteria can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as sine qua none". It is also interesting that he notes that too high value is put on statistical hypothesis testing which would not be needed when the results are clear.

Only the Hill-criteria strength of the relation, temporality and biological gradient can be judged from the study at hand without using other sources. The other Hill criteria relate to additional information such as in the analogy with other exposures criterion or other studies such as in the consistency between studies criterion.

Rothman has extensively elaborated causal inference in his text books on epidemiology [7,17]. He severely criticizes the criteria listed by Hill and concludes that "checklists lend a deceptive and mindless authority to an inherently imperfect and creative process of conjecture and refutation". One of the major problems in observational epidemiological studies is confounding leading to a spurious causal relation where there is none. The confounding factor or exposure is related to both the exposure and the outcome and explains the putative causal relationship. Rothman argues that all possible other explanations than a causal effect have to be conjecture. Only refutation of such a conjectured alternative cause in a new study contributes to the original causal inference. It is not difficult to see that without taking confounding into account a high relative risk does not lend more credibility to causal inference. The only important criterion from Hill's list that virtually always holds is temporality, because it is difficult to imagine how a cause that follows the effect could be causal.

Another authoritative and important source for causal inference can be found in the reports produced by the International Agency on Research on Cancer (IARC) [18]. The findings are reported according to a fixed framework and are based on both epidemiological, animal and other laboratory studies [19]. Causal inference is a two-step process in which, first, the quality of the evidence in the available studies is assessed and then, a conclusion is drawn on the causality, in this case the carcinogenicity, of the agent [20]. The first step, assessing the quality of the evidence is not very transparent. The whole process is fed by a group of invited experts, who make an arbitrary assessment of the quality of the evidence. The second step follows automatically from the quality of the evidence. When there is sufficient evidence from cohort studies, the agent will be qualified as carcinogenic. When there is sufficient evidence from animal studies but no epidemiological studies, the agent will be at most be qualified as probably carcinogenic. In their methods paper, IARC gives specific guidance on how to assess the quality of evidence relying heavily on the Hill criteria. Given the modern developments in systematic review methodology, it is difficult to understand why IARC still relies on a non-transparent expert and group process.

Epidemiologists should be the professional group that is aware of the pitfalls of causal inference. This led Holman et al. [21,22] to study how epidemiologists judge causal inference and to which pieces of information they attach the highest value. They constructed 12 case vignettes for the judgement of a hypothetical relation between a causal environmental factor and a disease. The vignettes all contained a varying level of the following parameters; strength of the association (relative risk [RR]), statistical significance (p-value), number of studies lending support, statistical coherence (dose-response relation), alternative explanations (confounders), study type (cross-sectional or cohort), specificity of cause and effect (more vs no other causes). The vignettes were assessed by 159 Australian epidemiologists. The variables were analyzed using a multivariate logistic regression analysis to study which factors influenced a decision of causality most. The strongest odds ratio was found for statistical significance. If studies had a very low p-value the odds of the epidemiologist making causal inferences was 7.2 higher (95% confidence interval [CI], 4.5 to 11.5) than when the studies had a p-value > 0.05. The next strongest factor was the adjustment for confounders with an odds ratio of 5.0 (95% CI, 2.6 to 9.6). Other significant variables were RR, number of studies, dose-response relation, and study-type.

Social Influences

So far, I have discussed the establishment of a causal relationship between work and disease from a scientific point of view. However, it will finally be policymakers who decide if and how a disease will be recognised as an occupational disease. Given the scientific uncertainties, this leaves ample room for stakeholders to be involved and influence decision making. Stakeholders are, among others, employers, trade or business

associations representing industry, trade unions representing employees, government officials and physicians. Dembe [23] studied the historical developments of cumulative trauma disorders, low back pain and noise induced hearing loss as occupational diseases. He was especially interested in how social factors affected the origins of these work-related diseases. He found more than a dozen social influences that played a major role, both enhancing and restraining, in the development of these diseases. The following are examples of such influences. The introduction of new technology, such as the telegraph led to an upsurge in telegraphers' cramp as an occupational disease. This did not happen when the typewriter was introduced, but it happened again when computers replaced typewriters. Aggressive marketing of hearing aids and audiometers in the 1950s brought increased attention to the problem of noise-induced hearing loss in workers. Interpretation of back pain as a traumatic injury corresponded with the growth of the orthopaedic speciality in the 1920s.

The recognition of a disease as an occupational disease is a political decision because it affects many stakeholders and can have great consequences for many parts of society. These decisions are never based on scientific evidence alone but take into account values, emotions, and economic consequences to name but a few. However, scientific evidence in general can make decisions more transparent. Where the scientific evidence is unclear, there is more room for other factors to influence the decision making process. This is the reason that, in some cases, industry has been caught in trying to deliberately create confusion about the scientific quality of the available evidence of an occupational disease [24].

Cases

Shift work and breast cancer

Shift work has been linked to breast cancer in both epidemiological and animal studies. The cancer risk is supposed to increase through exposure to light at night which disturbs melatonin metabolism. This in turn influences estrogen production which increases the risk of breast cancer. The epidemiological evidence has been summarized in several systematic reviews and in a report by the IARC. In a meta-analysis [25], the relative risk for breast cancer after exposure to shift work is reported as 1.5 (95% CI, 1.4 to 1.7). To examine the quality of the evidence, I will use the criteria given above; evidence for a disease, evidence for exposure, and evidence for a causal relation. A diagnosis of breast cancer is well defined and also in epidemiological studies, this is hardly a case for dispute. Exposure is difficult to measure, as an example; having worked in shift work is only a proxy for being exposed to light at night. There is a lot of uncertainty how well self-reported shift work represents exposure to light at night and better exposure measurement is called for [26]. For a causal relation at least the Hill criteria of a high relative risk, temporality and a biological gradient should be met. The relative risk is however low, it is unclear if cancer follows exposure and there is only an indication of a dose-response relation. According to Rothman the criterion for judging causality would be if we can bring up and refute other alternative explanations, such as confounders explaining the relationship. For breast cancer and shift work, there are several possible confounders such as obesity, alcohol intake, and regular exercise, all of which are related to both breast cancer and shift work. To my knowledge, there are no studies that have sufficiently taken all these confounders into account. The IARC approach has led to classifying shift work as probably carcinogenic (class 2A) but based this mainly on high quality evidence in animal studies. The IARC working group noted that there was a lack of convincing evidence in epidemiological studies due to potential confounding and exposure definition.

The various criteria for evidence of causality of epidemiological studies all point in the same direction that the evidence is at most moderate but not very convincing.

Aerotoxic syndrome

Aerotoxic syndrome has been put forward as a diagnosis for a cluster of symptoms experienced by airplane pilots and cabin attendants related to exposure to organophosphates especially tri-ortho-cresyl-phosphate (TOCP) is used as an additive in lubricant oil in a plane's engines [27]. The cabin air intake of a plane is closely connected to this system and a wearing out of the seals can lead to the contamination of cabin air with organophosphates.

I will again apply the three criteria for evidence of causality to this syndrome. The disease is not very well-defined as there is no case-definition and the measurement of symptoms is not standardized. The exposure can be measured and has been reported as being between 36 and 108 ng/m^3 [28]. This is however about a factor 10^6 under the time weighted average recommended as the threshold limit value reported by the American Conference of Governmental Industrial Hygienists for TOCP in 2008 with 0.1 mg to 0.5 mg/m^3 (www.acgih.org/tlv). Even though a very low exposure could lead to the reported symptoms, this is not probable. Theoretically, the TOCP might be an indicator of another yet unknown exposure that causes the symptoms. I have not found any cohort or case-control studies that could be proof of a relation. To present good evidence of causal relation, these studies should also take into account po-

tential confounders such as dry air, jet lag, perceived stress and long working hours that are both related to the symptoms and to the exposure in airplanes.

The various criteria for evidence of causality in epidemiological studies all point in the direction of a lack of evidence for a disease, of sufficient exposure and of a causal relationship. Well-designed epidemiological studies would be needed to fill this gap and underpin a decision about a work-related cause for the symptom cluster of the aerotoxic syndrome.

Conclusion

When assessing the evidence for an occupational origin of a disease three elements should be taken into account; evidence for a disease, evidence for exposure and evidence for a causal relationship. For the disease, consensus on symptoms, signs, and other tests is needed that together constitute the necessary elements of a diagnosis. For the exposure, evidence is needed that the used measures correspond well to objective exposure assessment. There are no absolute criteria for evidence of causality in observational epidemiological studies, but a wise application of criteria put forward by Hill and Rothman will make a causal relationship more likely or unlikely.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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