Commentary

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Can a causal relationship be established between acoustic neuroma and occupational exposure to non-ionizing radiations from mobile devices? Comparison between scientific literature data and medico-legal methodology

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Abstract

Background. Over the process of establishing the causal relationship, medical and legal methodologies may be at variance over the definitional standards and terminologies applied, which can hinder the activities of expert witnesses.

Objectives. The article's authors have set out to assess whether, and under what conditions, a causal relationship can be established between acoustic neuroma and exposure to non-ionizing radiation from mobile communication devices.

Methods. The study design is a Systematic Review. The authors have drawn upon a 2020 Turin Court of Appeals ruling which found such a causal relationship in a somewhat peculiar case: rare tumor and exposure to non-ionizing radiation of unusually long and regular duration. The case presents several peculiarities, herein analyzed in light of a) scientific evidence relative to the etiopathogenesis of the neuroma; b) available medico-legal literature defining causality evaluation criteria, and lastly c) court filings in regard to the probability standards applied to prove causal relationship.

Results. A direct tie cannot be proven, not even in cases of substantially intense and lengthy exposure, if the medico-legal standards applied are not consistent enough to prove that nexus is more likely than not.

Discussion. Several elements suggest a causal relationship is unlikely: a) a dearth of evidence on humans; b) rats exposed to such radiation have developed cardiac tumors, not in their ears; c) exposure has caused no tumors in mice; d) the length of exposure is incompatible with tumor size and type. That fourth point only concerns the case herein explored, whereas the first three have a general scope of validity. The main limitation of the present study design is the heterogeneity among the included studies. Retrospective and prospective studies have been included, which may be a source of bias. ***Clin Ter 2021; 172 (3):197-205. doi: 10.7417/CT.2021.2313***

Key words: *non-ionizing radiations, occupational exposure, acoustic neuroma, causal relationship, mobile devices*

Introduction

The increasingly widespread use of mobile communication devices has been growing in industrialized countries for at least two decades, both for personal and professional reasons. Many professional sectors indeed require workers to be in contact with colleagues who operate in different venues or even cities. Nearly constant professional use of mobile devices entails daily exposure to non-ionizing radiations, often for long periods at a time. An issue therefore arises of assessing the potential of such an exposure, particularly in work settings, to cause adverse health effects for workers.

The present article aims to closely focus on exposure to non-ionizing radiation originating from cellular phones and their alleged capability to cause acoustic neuroma.

The medico-legal concept of causal relationship

From both the conceptual and practical perspectives, it is essential to draw a distinction between "natural" causation, which pertains to the causal connections in the physical and biological realms, and medico-legal causation; the latter is closely focused on causal relationships between events and their subsequent repercussions, while disregarding those devoid of any legal relevance.

Such a distinction is itself frequently disregarded, which leads to the untruthful and erroneous outcome of ascribing causal value, in the medico-legal sense, to legally irrelevant natural events, i.e. legally immaterial.

Both under criminal and tort statutes, human conducts are criminally relevant, whether active or omissive, if they constitute the determining condition (*conditio sine qua non)* in the chain of events that contributed to the ultimate outcome, such as the condition that brought about the event resulting in damage (the so-called conditionalist theory).

As for practical applications, the determination process is usually conducted through a two-stage inquiry aimed at

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establishing factual causation (known by the English phrase but-for test), which breaks down as follows: a) human conduct is the event's determining factor, without which the ultimate outcome would not have occurred; b) human conduct is not the condition that brought about the event if such conducts can be taken out of the picture without changing the outcome.

Such an approach, however, can turn actions that could not have caused the event into contributing factors (1). As a consequence of that, particularly in terms of causal relationships interwoven with biological phenomena, the Italian Supreme Court has integrated the theory of conditionalism with one centered around the subsumption theory under scientific laws. Hence, a presumably triggering act can be viewed as a determining condition, i.e. cause, only if it falls into the category of events liable to cause developments such as the one that actually took place; such a determination needs to be based on a regular succession, in conformity with a rule grounded in practical experience or scientifically validated - "covering law model"-, according to the best experience and science at a given historical time (2, 3).

Such models may be universal or statistical in nature. According to the Italian Supreme Court, medium-low coefficients of statistical probability (and even more so empirical generalizations of common sense or epidemiological findings) undoubtedly call for thorough and timely verification procedures with respect to scientific evidence and specific applicability to the case at hand. Nothing however rules out their fitness to be used for causal relationship verification, as long as medico-legal verification criteria are met which rule out the incidence of other alternative determining factors.

On the contrary, high levels of statistical probability require courts to verify the etiological value in light of all circumstances pertaining to the event itself, although they may unveil a regularly occurring, statistically significant chain of events. Such circumstances may include the absence of alternative explanations. That pattern gives rise to the transition from statistical to logical probability, which the Supreme Court has tasked the expert witnesses with evaluating in occupational disease cases, among others (3, 4).

Common law jurisprudence itself is somewhat leery of proving causal relationship through statistical data (5, 6). Undoubtedly, the soundness of epidemiological findings rests upon the relative degree of probability; still, according to several scholars, there is no reason to foreclose the possibility that epidemiological data may be enough to prove a causal relationship, based on the so-called "More likely than not" standard (7, 8).

Acoustic neuroma

Acoustic neuroma (AN) is a rare, benign tumor that arise from the Schwann cells of the nerve sheath surrounding the vestibulocochlear cranial nerve (VIII CN). It is a slowly growing tumor that develops in the inner ear and gradually expands to the cerebellopontine angle with potential compression of the brain stem.

Symptoms include unilateral hearing loss, tinnitus and dizziness The median age at diagnosis are 50 years or more, except for rare tumors that occur in patients affected by neurofibromatosis type II (NFII), which are often diagnosed in younger persons with 90-95% lifetime risk. Due to the slow growth rate of AN, in many cases the definitive diagnosis is made several years after the onset of the first symptoms. Women are generally affected more than men, with a sex ratio close to 1.3.

Treatment strategies are surgery and radiotherapy, both potentially related to persistent disabling symptoms after treatment such as hearing loss, tinnitus and facial paralysis.

ANs represent about 5% of primary central nervous system tumors and 63% of tumors of cranial and spinal nerves with estimated incidence of 1–20 per million population per year in most industrialized countries.

Acoustic Neuroma and Cellular Phone. Etiopathogenesis

The etiology of acoustic neuroma is largely unknown.

The increased incidence of AN over the recent decades can be partially explained by advanced diagnostic tools, better access to CT and MRI and increased awareness of the disease.

However, a number of environmental causes has been suggested as risk factors of AN development, such as exposure to ionizing radiation during childhood, loud noise at work and female hormones.

Even Radio Frequency Electromagnetic Field (RF-EMF) has been suggested as a potentially risk factor and it has been debated whether RF-EMS could initiate or promote cancer.

From 2000 till 2004 the REFLEX project was carried out to investigate genotoxic effects of RF-EMF using sensitive *in vitro* methods. A significant increase in single and double strand DNA breaks has been demonstrated, as well as micronuclei frequency at specific absorption rate (SAR) levels between 0.3 and 2 W/k. Significant findings of chromosomal aberrations were observed in fibroblasts and intracellular increase of free radicals in HL-60 cells. (9,10)

Mobile phone use has increased rapidly since 1980s, with an estimated 7,68 billion mobile phone subscriptions globally, according to the International Telecommunication Union (2017). Cell phones and other commonly used wireless communication devices transmit information via non-ionizing radiofrequency radiation (RFR).

There has been public concern about the possibility of adverse health effects resulting from exposure to RF-EMF, particularly in the development of intracranial tumors. (11,12)

Among head and neck tumors, acoustic neuroma is of particular concern due to the proximity of the tumor location to the antenna area.

RF energy absorption-rate (SAR) values in the brain depend on the design and position of the phone and its antenna in relation to the head, how the phone is held, the anatomy of the head, and the quality of the link between the base station and phone. Electromagnetic radiation from a cell phone is attenuated by more than 90 percent within 4–6 cm.

Moreover, it should be noted that the average exposure from use of digitally enhanced cordless telecommunications (DECT) phones is around five times lower than that measured for global system mobile communications (GSM) phones, and third generation (3G) phones emit nearly 1/100 RF energy compared to GSM phones (13)

In May 2011, a working group of 30 scientists from 14 countries at the International Agency for Research on Cancer (IARC) classified RF-EMF as 'possibly carcinogenic to humans' (Group 2B) based on limited evidence both in humans and experimental animals. Human exposures to RF-EMF (frequency range 30 kHz–300 GHz) include radiation from mobile phones, from occupational sources (e.g. high- frequency dielectric and induction heaters, and high-powered pulsed radars), and from environmental sources such as mobile-phone base stations, broadcast antennas, and medical applications. (14)

The IARC group conclusions were based on limited evidence from epidemiological and animal studies for an association between use of mobile phones and the risk of glioma and acoustic neuroma.

A lot of epidemiological studies have been reported to confirm this association (15,16) but some studies didn't show a significantly increased incidence of acoustic neuroma among users of mobile telephones. (17,18,19)

In light of need for further confirming evidence, the International Agency for Research on Cancer had promoted a large-scale epidemiological case-control study, called INTERPHONE study, including sixteen study centers from 13 countries. The combined analysis of the INTERPHONE study is based on the largest number of AN cases and, in particular, the largest number of long-term mobile phone users reported to date (20). This international study was supported by funding from the European Fifth Framework Program, 'Quality of Life and Management of Living Resources' and the International Union against Cancer (UICC), that received funds for this purpose from the Mobile Manufacturers' Forum and GSM Association.

Before the publication of interphone study results, preliminary data have been published.

Studies conducted in Denmark (18) and Japan (21) have found no increase in the risk of acoustic neuroma associated with mobile phone use.

Otherwise, Lonn et al in 2004, observed an increased risk of acoustic neuroma for mobile phone use on the same side of the head for at least 10 years duration with an odds ratio of 3.9 (95% CI, 1.6–9.5), while no risk increase was found for short-term mobile phone use and a short latency period. (22)

Shoemaker et al. have conducted six population-based case–control studies within the Interphone collaboration with 678 cases and 3553 controls, in the UK and four Nordic countries. Their findings do not support an increased risk of acoustic neuroma in the first decade after starting mobile phone use, but they confirm an increase in risk for ipsilateral use of mobile phones for 10 years or more, of uncertain interpretation. (23)

It should be noted that the association between long-term mobile phone use (10 or more years) and acoustic neuroma found in the Swedish INTERPHONE was not confirmed in the larger pooled analyses of INTERPHONE studies, published in 2011. They did not see any trend in AN risk with increasing cumulative use but there was an increased odds ratio for those with heavy cumulative call time (1640 h or more), particularly long-term users and those who reported mobile phone use on the same side of their head as the tumor occurred.

Otherwise, Hardell group in previous epidemiological studies have found an increased risk of brain tumors associated with cellular phone, particularly for acoustic neuroma and for the side of the brain where the cellular phone had been used.

In 2005, Hardell et al. performed a case-control study in which they showed that during calls with cellular or cordless phones, the brain is exposed to microwaves in the range of 400–2,000 MHz with the highest exposure being on the temporal area, due to physical properties of the phone. (10)

In 2009 the same group reported a relative risk of 2.9 (95% CI 1.6–5.5) for acoustic neuroma associated with the use of mobile phones for more than 10 years. (24)

The results of an association between use of mobile and cordless phones and acoustic neuroma with risk increasing with increasing duration of exposure, were confirmed by subsequent studies. (25,26)

Case–control studies are known to be vulnerable to selection and recall biases, especially for mobile phone use occurring a long time before the diagnosis.

Selection bias of case-control study distorts estimates of risk when participation of cases and controls is affected differentially by the status of mobile phone use. Recall bias distorts estimates of risk

when the recall of past mobile phone use is differentially biased among cases and controls. Recall bias for the ear more frequently used for mobile phone use in the past is of particular concern as the side of phone use is often presented as evidence for causality if coinciding with side of acoustic neuroma (19).

With the aim to reduce possible bias, Yasuto Sato et al. conducted a case–case design, to investigate the association between various parameters of mobile phone use and the risk of acoustic neuroma, taking into account the more frequently used ear and the location of acoustic neuroma. (27)

They have considered the affected ear as the case side, while the opposite ear as the control side. The case–case study is also vulnerable to selection and recall biases, but the situation is less complicated than in case–control studies because the same patient plays the role of both case and control.

They identified no significant increased risk for regular mobile phone use compared to non-use, use until 1 year before diagnosis and use until 5 years before diagnosis. Increased risk of acoustic neuroma was, instead, observed in cases who reported having used mobile phones on the affected ear for >20 min/day on average.

The Canadian data from the case-control Interphone Study have undergone a re-analysis from Momoli et al. in 2016. (28)

They conducted a probabilistic multiple-bias model to address possible biases simultaneously, using validation data from billing records and nonparticipant questionnaires as information on recall error and selective participation. In contrast to the previous Interphone publications in which bias in sensitivity analyses was addressed with individual simple adjustments, they have attempted an approach to bias-adjustment in order to provide a single set of potentially more causally interpretable results after correcting for 2 possible biases simultaneously.

Using a logistic regression modeling strategy different from that used in previous studies of Interphone data and based on a subset of the Interphone data set, they found results that were broadly consistent with the range of results observed in the entire international study for meningiomas and acoustic neuromas.

After adjustment for selection and recall biases, little evidence was found of an increased risk of meningioma, acoustic neuroma, or parotid gland tumors in relation to mobile phone use.

Recently, a systematic review of multiple electronic data bases for relevant publications, support the hypothesis that long-term (over 10 years) use of mobile phone increases risk of intracranial tumors, especially in the case of ipsilateral exposure. (29)

Despite the results obtained from several studies, the IARC Working Group deemed the overall evidence as inconclusive based on epidemiologic and animals studies.

With the aim of investigating RFR carcinogenicity, US National Toxicology Program (NTP) conducted a large systematic and integrated experimental project on RF, including in vivo long-term bioassays in Harlan Sprague-Dawley (HSD) rats and B6C3F1/N mice exposed to RF from prenatal life up to 2 years in the situation of near field, reproducing the exposure to RF generated by the antenna of mobile phone. The two main RFR modulations used for cellular telephone communication worldwide, CDMA and GSM, were tested. (30) RFR exposure is known to potentially lead to temperature increases in biological tissues and if excessive, can result in the disruption of thermoregulation in animals. However, these effects depend on the animal characteristics (age, size, species, and strain) and parameters of the RF signal (power level, frequency, modulation). (31)

Based on the experiments, the NTP concluded that results showed clear evidence of carcinogenic activity of cell phone RFR (both modulations) based on increased incidence of malignant glial tumors of the brain and heart Schwannoma in rats exposed to GSM and CDMA modulated cell phone. (32)

The observation that cell phone RFR affects heart and brain tissue in Sprague Dawley rats after long-term exposure was confirmed in a similar study by the Ramazzini Institute (RI).

In 2005, RI started a life-span carcinogenic study on Sprague-Dawley rats to evaluate the carcinogenic effects of RFR in the situation of far field, reproducing the environmental exposure to RFR generated by a 1.8 GHz GSM antenna of the radio base stations of mobile phone. They conducted a large long-term study in 2448 animals on the health effects of RFR, reaching similar conclusion to the NTP study. The RI findings on far field exposure to RFR are in fact consistent with the results of the NTP study on near field exposure to RFR, as both reported an increase in the incidence of tumors of the brain and heart in RFR-exposed Sprague-Dawley rats. (33)

These recently reported experimental studies provide sufficient evidence for a re-evaluation of IARC conclusions regarding the carcinogenic potential of RFR in humans. (34)

Neuroma (or schwannoma) of the eighth cranial nerve can occur as a rare tumor or as part of Neurofibromatosis 2 (NF2), an autosomal dominant disease that predisposes to develop of cranial and spinal tumors including schwannomas, meningiomas, and ependymomas with full penetrance. (35) A causative germline mutation in the Neurofibromin-2 (NF2) gene can be identified in 70 to 90% of the affected patients; the presence of large deletions, mutations in promoter or intronic regions, and somatic mosaicism often hinders the identification of the exact mutation. (36) The NF2 gene encodes for a cytoskeletal tumor suppressor protein named Merlin (myosin, ezrin, radixin-like protein). The role of NF2 gene mutations in the neurofibromatosis 2 is known, but more recently a deregulation of the Hippo pathway has been demonstrated, caused by Merlin-mediated suppression also in human sporadic schwannoma. The deregulation of the Hippo pathway is not fully understood but the evidence strongly shows multiple aberrant genes expression of Hippo core components and regulators in schwannomas without NF2 mutation, which suggests that other mechanisms may affect activation of the Hippo pathway and result in tumorigenesis of schwannomas. (37)

Ionizing radiation exposure has itself been suggested as risk factor of sporadic neuroma development. Several cohorts and sporadic case reports confirm this association. (38) More recently, a linear dose-response relationship has been reported for acoustic neuromas that strongly supports a causal role for radiation even after the fourth and fifth decades after the exposure. (39) Speaking of ionizing radiation and the causal link with the onset of neoplasms, it is important to underline the relatively recent acknowledgement by the European Union which, with a Directive of 2013, imposed on Member States new indications to improve the protection of the population from the possible risks arising from the exposure to radiations in health care, work, and social settings (40).

Medico-legal standards in the assessment and establishment of causal relationship

The most commonly applied medico-legal assessment standards of causal relationships are subdivided into chronological, qualitative, quantitative, modal, phenomenological continuity, scientific likelihood, statistical-epidemiological, and exclusion of other causes. When assessing a specific case, causal relationship analysis requires the application and integrated study of all said standards, which must all converge towards the ultimate judgment of admission or exclusion of the causal relationship.

The cause has to have occurred prior to the effect. Nonetheless, such a trait is not enough to meet the chronological standard. To that end, the time length that has gone by between the preceding event and the subsequent damage has to be long enough, according to applicable scientific knowledge for the establishment of a causal relationship.

Hence, the chronological standard must comprise incubation and latency periods as well, which means an analysis as to the actual suitability of that which practically took place and is validated by scientific knowledge on that given topic at that point in time. That line of thought holds particular relevance in regard to the case analysis herein outlined, since tumors are deemed belated causality injuries. It is therefore essential to assess the length of the exposure to non-ionizing radiation.

The qualitative standard is constituted by the vetting and comparison of all qualitative characteristics presented by the harmful event, in addition to those inherent to the damage-related consequences, so as to prove the nexus between them.

Quality is closely related to the specific traits of events, harm causing tools, pieces of evidence, outcomes, etc.; such traits are indeed instrumental in distinguishing each one of those elements from others. It is therefore necessary to prove compatibility between acoustic neuroma's qualitative traits and non-ionizing radiations.

A quantitative set of criteria needs to be applied to the strength through which the injury has been produced, as well as to the degree of organic resistance of the inured party and to the number of harmful events brought about by the harm causing tool itself.

At any rate, the scope of the damage stems from two distinct quantities: the energy exerted to the harm causing tool and the organic resistance opposed to it. By virtue of that, in the cases herein analyzed, it is necessary to assess the daily amount of non-ionizing radiation from mobile devices, to which the patients have been exposed.

The modal standard calls for a verification of the match between the location where the trauma was brought, the harmful modality of traumatic strength, the ways of production, manifestation and evolution of each injury, its specific characteristics, and outcome consolidation. Such criteria cannot be fully assessed however, since the way in which non-ionizing radiation act on human organisms is still unknown by and large, other than rather its generic inflammatory effects. Nonetheless, the match between the onset of the tumor and the ear exposed to the radiation through the device used by the patient needs to be ascertained.

In accordance with the phenomenological continuity standard, a continuity must have taken place in terms of disease manifestations over time, from the very start of the harmful action to the outcomes thereby generated. A close connection may thus come to the surface between that standard and the modal and chronological ones.

The scientific possibility standard is based on an in-depth analysis of scientific literature and constitutes the cornerstone of any causal relationship examination: if the scientific vetting of any given case corroborates the possibility of an etiological relationship, medico-legal methodology requires setting in motion a further process of verification as to the causal hypothesis; ascertaining the mere possibility, in fact, only means that such a hypothesis cannot be foreclosed.

The epidemiological-statistical criterion is closely linked to such a principle as well, in that it focuses on the correlation between specific antecedent and subsequent events, by verifying how frequently a given antecedent event is matched by a specific subsequent event, and how any

modification in the antecedent occurrence leads to a similar change in a subsequent one. The more such a match can be proven and verified, the more likely is the causal relationship to be confirmed. In fact, when an antecedent event is always matched by a subsequent development, the causal relationship is bound to be acknowledged by universal law.

The relevance that such a standard holds is therefore indisputable: it constitutes the inception of any subsumption assessment according to the laws of science as reported above. Statistical data however, as mentioned before, need to be evaluated along with all other criteria, in order to make sure whether they are bolstered by other circumstances in the case in point (1).

Exclusion criteria relative to other causes are aimed at verifying whether the case at hand has stemmed from causes other than the ones considered up to that point. Should an affirmative answer be found, the event should be considered caused by all the parties that had contributed to the various causes. The only exception, both in Italian statutes and in Common Law, has to do with cases in which one of the multiple causes is found to have been enough to cause the event itself. In such instances, the event ought to be ascribed, from a causal standpoint, only to those from whom that cause had arisen (41).

Hence, exclusion criteria is tantamount to ruling out that the first or new injuries have played a role in causing the harmful event; foreclosing the possibility that such injuries may have worsened the others; ruling out that the death or objectivized functional impairment may have or must have traced back to causes other than traumatic ones, brought about by the first or second trauma, etc...

It is also quite manifest that a sound application of such criteria would require a thorough determination of the whole chain of events, from the standpoint of biological-clinical phenomenology, which from given injuries lead to specific outcomes (1).

Standards of proof for the determination of causal relationship

Standards of proof applied in tort law proceedings for the assignment of compensatory damages in Common Law countries hinge on principles such as "Greater weight of the evidence", "More likely than not", "Actual belief" or "Balance of probabilities".

The first one, also known as "Preponderance of the evidence", is applied much like a scale would work: by setting on one side all the evidence in favor of the damaged party and that favoring the defendant on the other, which party will prevail is established by whose favor the scale will be tipped in, however slightly, based on the believability or persuasiveness of evidence.

According to the "More Likely Than Not" principle, an event is deemed to be proven if through an assessment of all evidence provided, it is adjudicated more likely to be true than false, by virtue of an over .5 probability level.

The two principles above described do not necessarily dovetail. The evidence gathered by the plaintiff in his/her favor may in fact be more than that in favor of the defendant, and yet the inconsistency of the former may lead a court to conclude that the plaintiff's argument is more likely to be false than true. In fact, based on the "Greater weight of the evidence" principle, plaintiffs can prevail if they succeed in proving that their arguments and statements are more likely and plausible than the ones laid out by the defendants. On the other hand, according to "More likely than not" standards, plaintiffs need to prove their version more likely to be true

than false. Hence, the standard of proof required under the "Greater weight of the evidence" principle is lower than the one in place under the "More likely than not" approach.

The "Actual belief standard" posits that triers (jurors or judges, depending on each judicial system) should determine whether a fact is provable based on whether they are willing to believe it and that the evidence corroborating a given thesis outweighs proof to the contrary.

It is not a mere variation to the "Greater weight of the evidence" standard. If one single scientific publication, for instance, is found to support the existence of a causal relationship between an event and a given harmful agent through research practices of subpar quality, and yet such a nexus is not rebutted, the "Greater weight of the evidence" principle could lead to the plaintiff being awarded compensatory damages, since no evidence to the contrary has been found. Nevertheless, based on the "Actual belief" standard, an opposite conclusion should be drawn, because the poor quality of the research supporting that causal relationship is not credible enough. The "belief standard" is at variance with the "more likely than not standard" as well. As a matter of fact, it is plausible to believe that statements by a witness or a scientific publication is more likely to be true than false, while at the same time still being unwilling to believe in said witness or in the publication's authors.

The "Balance of Probabilities" standard is applied in the United Kingdom and other Commonwealth nations, although in such a way as make it quite similar to the "More likely than not" principle (42).

The Italian Supreme Court has outlined the reasoning at the root of the evidence establishing process: firstly, judges are supposed to assess any piece of evidence in an analytical fashion, so as to discard those essentially devoid of any relevance and to keep those which meet the fundamental criteria of precision and substantiation, i.e. hold a partial, or at least potential, evidentiary weight and effectiveness; at a later stage, courts will have to lay out a comprehensive assessment of all presumptive evidence on an isolated basis, and ascertain their homogeneity and whether their combination may be capable of providing viable evidence that could not be achieved with any degree of certainty by considering each evidentiary element separately (43). Such an assertion is based on article 2729 of the Italian civil code, according to which evidence for any event may be attained through evidentiary elements, provided that they are overwhelming, accurate and in agreement with one another.

That rationale does not foreclose resorting to the probability-based standard, but rather binds it to the relevance and agreement of all relevant circumstances pertaining to the events on trial. In fact, «it is not necessary for the existence of an unknown event to be the only consequence possible, according to a connection based on absolute and exclusive necessity; it is enough, on the other hand, that the unknown event can be inferred from the known facts, not unlike a probability- based judgement grounded in the "id quod plerumque accidit". Conversely, the evidentiary value of an inference merely based on hypothetical elements should be ruled out (44). Hence, it can be argued that the Italian Supreme Court itself routinely applies the "More likely than not" standard (45).

Such an issue lingers, with an even greater degree of complexity, when multiple causal explanations exist as to the harmful event itself. Part of Italian literature seems to point to a lower level of probability in order to prove a causal relationship when multiple causal explanations exist; in fact, the "more likely than not" standard entails that courts deem to be "true" the argument or version that can be proven by relying on the higher level of available evidence in its favor (46).

Nevertheless, such a conclusion can be shared as an expression of the "Greater weight of evidence" principle, rather than "More likely than not". The latter, as we have already pointed out, does not pit the level of credibility in the plaintiff's argument against the defendant's, but rather requires either case to be more likely true than false (47).

A very recent and highly debatable assertion from the Turin Court of Appeals in regard to existence of the causal relationship

In 2020, the Turin Court of Appeals (48) has upheld a ruling that had sentenced the National Insurance Institute against occupational injuries to pay compensatory damages to a worker, holding that the vestibular schwannoma (along with a 23% permanent damage) had been caused by the radiation emitted by the mobile device used by the worker on duty.

Provided that when it comes to civil liability, the causal relationship is generally established based on the "more likely than not" criterion, the court has acknowledged the causal relationship by virtue of that specific case's peculiarities: a linkage between a rare tumor and exposure to radiation, unusual for length, regularity and intensity; a period of latency compatible with the values ascribed to non-epithelial tumors; the fact that the disease had started in the right side of the plaintiff's head, who was right-handed; the lack of any plausible alternative explanation for the disease onset.

As for the time length, witnesses testified that the plaintiff was required to use the phone for roughly four hours on a daily basis, for a period spanning from 1995 to 2010, with an overall estimate of 840 hours per year, for 15 years.

The degree of exposure intensity had been egregiously high, due to the very types of devices being used (ETACS, GSM 2G, with emission levels over 100 times higher than modern devices).

As for the allegedly low degree of reliability of the studies centered around the carcinogenic effect of non-ionizing radiation, given that they are not based on human trials, the court found it not to be enough to conclude that the causal relationship was unlikely. In fact, according to the judges and the court-appointed expert witnesses, carcinogenicity testing is conducted on animal models because experimental data have shown that any carcinogenic agent for humans has been found to be so in animals as well, when adequately tested; moreover, almost a third of human carcinogens have been identified after their carcinogenic effects had been observed thorough animal testing. Nonetheless, such a reasoning only proves that what is carcinogenic for humans is for animals as well, whereas in the trial it was necessary to prove, conversely, that animal carcinogens have the same effects on humans too. In that respect, the court only stated

that there was no reason to believe that a "physical agent" such as radiofrequency radiation can be harmful to animal organisms and harmless to humans. Testing centered around the alleged carcinogenicity of agents or substances is usually carried out on animals, mostly rodents, which present considerable similarities with humans; hence, the scientific value of such studies cannot be summarily denied. Still, in trials, the causal relationship that has to be proven is not the one with generic damages, but rather with specific diseases. Consequently, since an evaluation standard of the causal relationship itself is the qualitative standard, it is necessary to verify the compatibility between the type of harmful agent (non-ionizing radiation from mobile devices) and the type of cancer for which compensatory damages are sought.

In that regard, the rats that were exposed to such radiation developed cardiac schwannomas, which are akin to acoustic neuromas, from a histological perspective (the latter are in fact properly termed vestibular schwannomas); that connection seems to bear out a causal relationship between the exposure to radiation and the development of acoustic neuroma. After all, the fact that the acoustic neuroma is a benign tumor, unlike the malignant cardiac schwannomas observed in the rats, was deemed irrelevant, since such studies have proven that exposure to radiation can bring about the neoplastic transformation of Schwann's cells: such a process occurs in both benign and malignant tumors;

The court also disregarded the fact that in the rats, exposure to radiation had resulted in cardiac schwannomas rather than brain tumors. Such a discrepancy can in fact be explained by the fact that the rats were exposed to radiation all over their bodies, not only to their heads, as it usually happens when operating cell phones.

The court also deemed irrelevant, baselessly in our view, the fact that the high incidence of cancer had been found in rats (almost exclusively male rats), yet it was not observed in mice. It is difficult to comprehend on what grounds did the court establish that the human body would necessarily react to non-ionizing radiation the way rats do, rather than mice.

The chronological criterion constitutes an issue in the case analysis as well. The court asserted that the acoustic neuroma is a rare, benign, slow growing brain tumor, with a latency period of no less than 10-15 years between exposure to risk factors and diagnosis.

In 2010, the plaintiff's tumor had a 2.6 cm size, with a growth rate of roughly 1.5 mm per year, according to INAIL appointed experts. Consequently, in light of the latency period, the tumor already existed when the exposure started. In that regard, the court remarked that the 1.5 mm yearly growth refers to roughly 75% of acoustic neuromas, whereas 25% of them have a tendency to grow considerably faster, and in a more aggressive fashion. Acoustic neuroma cases also entail cystic and intratumoral haemorrhage (which occurred in the plaintiff's case), and growth rates of over 4 mm per year (49), and as much as 25 mm per year. It can therefore be inferred that only 25% of cases have growth rates compatible with the specific case's latency period, which should make a causal relationship seem less likely.

The Turin Court of Appeals seems to have espoused the rationale based on the "greater weight of the evidence" principle, which is quite commonly applied in American jurisprudence, although the judges later declared to have followed the "more likely than not" standard. It is worth noting that the conflict of interest that could be found in the literature supporting the lack of causal relationship made such proof less persuasive than those brought by the claimant, which on the contrary were based on research untarnished by conflict of interest. The court appears to have compared the degree of believability of each piece of evidence brought by the parties involved. Nowhere in the court's reasoning did the judges address the issue of whether it was more likely true or false that acoustic neuromas can be caused by exposure to non-ionizing radiation for a number of hours during workdays, over a 15-year period.

The scientific tenability of the causal relationship itself seems somewhat lacking. The court in fact based its conclusion on trials carried out on rats, which however developed malignant cardiac tumors, not benign neuromas. Furthermore, a generalized parallel between radiation effects on rats and men seems to be rather prejudicial, and so is, in our view, the demonstration of alleged quantitative standards and criteria for the exclusion of other possible causes. As for the former, only in a minority of cases is the tumor compatible with the duration of exposure in the specific case. As for the latter aspect, jurisprudence herein cited has clarified that whenever a causal relationship has a low likelihood level, only the total untenability of alternative causal thesis can warrant a conviction. In the specific case, on the other hand, the possibility that the neuroma might have been caused by neurofibromatosis type 2 had never been taken into account. In addition, a dearth of scientific knowledge as to the etiopathogenesis of neuroma makes alternative causal explanations possible.

Conclusions

The solution of specific cases, such as the one explored herein, is undeniably influenced by the choice of any given evidentiary standard. Still, even by applying a standard, as Italian courts do with the "more likely than not" method, conclusions may come out different, even opposed. The criticism leveled at the ruling in that case has highlighted the possibility to reach conclusions radically opposed to the ones laid out by the court.

Another relevant element of uncertainty regarding the trial's ultimate outcome has to do with the selective, partial application of different medico-legal methodologies. All methodological approaches should have been in our view thoroughly eviscerated and fully taken into account, though not all with full certainty, in order for a causal relationship to be ascertained. By drawing upon the analytical method conducted by Leubsdorf with regard to the foundational elements of liability and applying it to the medico-legal criteria for causal relationship assessment, it is noteworthy that it is enough for just one standard to have low probability levels to cause the overall logical probability to go below 50%.

Hence, despite the objective inability to consider the causal relationship demonstrated, the above reported court ruling constitutes a red flag for employers, medical specialists and prevention and protection system officials; all such profiles are in fact charged with assessing and reducing the

risk for worker health. Best practices should therefore be espoused (50,51), enshrining a set of cautionary rules aimed at providing protection for workers during prolonged exposure spells. Otherwise, despite the possible liability of the doctors in charge is extracontractual in nature (52), a less than thorough process for verifying the causal relationship could result in them being held liable.

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