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Types of epidemiological studies

Dr Varela: Thank you very much. Good evening my dear colleagues. I thank you all for watching. And also, I'd like to thank the European School for inviting me to share in this topic with you and also to Professor Bertolaccini for chairing this session. I'd like to start my talk saying that for me, clinical epidemiology has been a nightmare at the beginning of my professional practice. Too many different types of design, too many mathematics and statistics, and I was not an expert on that, until the moment I localized, in a book store, this wonderful book, "Interpreting the Medical Literature", I was not reading the fifth edition but probably the second one. I'm not trying to sell this book. But I'm just encouraging you to read on this topic, because in this talk, I'm offering to you a rather simplistic and quick view of this topic. I'm not trying to be exhaustive and reviewing any kind of design, or the statistics needed, because, as a clinician, you don't need to know a lot about statistics. What you need is treating well your patients, operating rightly or treating your oncological patients or whatever. So, leave mathematics for mathematicians. So, my recommendation is reading this or a similar book. According to this book, the study designs can be divided into descriptive, these are aimed just to describe a phenomenon; and explanatory, these are trying to find correlations, explanation to a clinical phenomenon, to a reason for a complication or whatever, while these ones are just describing. Let's forget these ones for a moment and let's focus on descriptive studies. This is an example describing one single case. In this case, the authors are presenting to readers the case of an elderly patient surviving COVID infection and lung cancer. This is just showing to you what happened in their practice. They found this case and the outcome was that and that happened to the patient. But look at this. In this case, the authors choose an appealing title because if the title is simply "Elderly patients surviving blah, blah, blah", your position is, "So what?". But if they add two words at the beginning of the title, this seems to be more interesting. So, my recommendation, whenever you're trying to publish a description of one single case, try to find a title which is resulting appealing to readers. These are rather difficult to publish. You can try to publish a case series. Case series are trying to show feasibility of a therapy or a procedure, and safety. This is a good example of feasibility. Video-assisted thoracic surgery is feasible for sleeve lobectomy. You're not comparing, you're not comparing sleeve lobectomy to open lobectomy or induction chemo to sleeve lobectomy or whatever, you are simply describing. So, no conclusions can be drawn for these kinds of papers. In this other paper, "Video-assisted thoracic surgery for lung cancer in octogenarians", you're trying to show to the readers that video-assisted thoracic surgery is safe, in your practice, in octogenarians having lung cancer, but no conclusions can be drawn for these two papers, just you're showing to the audience or to the readers that this can be done and these are my results in my practice. Going back to the Gehlbach book, you can find explanatory studies. Explanatory studies are divided in experimental, where you assign a subject to a group, to chemotherapy, to radiotherapy, to surgery, to induction, to whatever, and observational, you're not assigning patients. You are just observing what is going on with your cases. In experimental studies, the investigator is controlling the

exposure of the patient to something: to therapy, to surgery, to whatever, and you want to discover a causal relationship. This is aimed to investigate the causes. This, if I am permitted to say, is the king of design, but in surgical practice, reviewing four top surgical journals in the USA and the UK, just 5% are randomized clinical trials. And along the time, most of these randomized trials are sponsored by medical or pharmacological companies because they are super expensive and a good design is not accessible to most of us who are surgeons, oncologist, internist or whatever. Remember, you can ask your questions. So, take note of your questions and asking, you're kindly invited to ask your questions at the end. This is an example of randomized clinical trial. The investigators are comparing this new therapy on the standard therapy for stage IV non-small-cell lung cancer in what is called a phase III randomized trial. And they conclude that the new therapy offers 10-months of survival versus 9-months in the standard therapy with a P value under 0.05. My problem is, is that really relevant from a clinical point of view? Please read this paper. In this paper, the authors are explaining that a randomized trial should have clinical relevance and naturally P values under 0.05. In the previous article I'm showing to you, what is the real relevance in metastatic lung cancer stage IV? It's making sense, a survival of 10-months versus 9-months. I'm not sure, maybe yes, but probably not. Let's go to observational studies. In these cases, they investigator is just observing what is happening in a series of cases to discover association, not causes, and they are aimed to define new hypotheses. Three different types, cross-sectional, case-control studies and cohort studies. Let's go to cross sectional. These are called also prevalent studies. These are cheaper and quicker and rather easy to design, but they are usually biased, less conclusive and they are useful just to hypothesize. This is an example, "Prevalence of pulmonary nodules on CT scan of the thorax in trauma patients." In these series, the authors just report that in a series of, for instance, 20 cases, they have found 3 cases of pulmonary nodules, 15%. This is interesting maybe to hypothesize that in your clinic, maybe, if you've indicated CT scan on elderly patients or smokers or whatever, pay attention to pulmonary nodules or whatever, but you cannot conclude more. Case-control studies are also cheaper, can be organized quickly and performed quickly but usually are biased and you can conclude on association, not on causes. So, in these cases, we begin with people having the outcome already, for instance, pneumonia or hospital readmission or whatever the outcome is. And we compare them to subjects who do not have the outcome. And you try to find a correlation with a supposed risk-factor. You are hypothesizing that neoadjuvant, for instance, is responsible of pneumonia in your series or readmission or bronchial fistula or whatever the outcome is. So, you start having patients with or without the outcome and then you go back to your series to investigate the rate of patients having risk-factor or having not risk-factor in both series with outcome-positive or outcome-negative. Let's see this example. This paper, the title is "Prevalence of Venous Thromboembolism in Thoracic Surgery." And the authors describe in pneumonectomy cases, 4 out of 300 cases had pulmonary embolism, while in lobectomy cases, only 3 out of 1,300 had pulmonary embolism. They conclude there is a high probability, a higher probability of pulmonary embolism in patients after pneumonectomy and they measure the probability in the statistical odds-ratio which is calculated this way, multiplying in cross and dividing this way. It's a very, very simple calculation, you can do it with your mobile phone. This would be the right title for this manuscript. Pay attention always to the title in your manuscript. If you just state "Prevalence of pulmonary embolism" you're not offering the right view of your investigation to the editor of the paper, so, this would be a much better title. "Risk of pulmonary embolism is higher after pneumonectomy compared to lobectomy." Because this is abstracting the whole paper you're willing to published. In case-control studies, you're showing association, not causes. Look at this paper, the title is very well elected. "Association between environmental tobacco smoke exposure and lung cancer" in this kind of polymorphism. The authors conclude that the presence of this polymorphism in patients appears to enhance the magnitude of association between lung cancer and exposure to tobacco smoke. This is the only conclusion. Apparently, there is a correlation, but you never know if the cause of lung cancer is tobacco exposure or not. Remember, think about your questions for the end of the presentation. A step ahead is matched cases and controls. The risk when you're dealing with cases in controls is that you can compare pears and apples. In this case, "Early outcomes of robotic versus thoracoscopy segmentectomy" the authors are matching thoracoscopic and robotic cases. It is not the same comparing thoracoscopic and

robotic if patients are elderly or heavy smokers or having a very low FEV1 and so-and-so. So, for matching cases and controls, you must compare comparable surgical skills, comparable perioperative care and so, and so, and so, but patients have a different technique. But the patients are not randomized to receive thoracoscopic or robotic, so, you are not influencing the selection of thoracoscopic or robotic. You are just analyzing your series of cases. If the outcome is associated, not to one single variable, pneumonia readmission, developing lung cancer, but a set of variables, then you're performing a multivariate analysis. This is this case, "Emergency hospital readmission after major lung resection: prevalence and related variables." In this case, the authors are having a group of patients and they go back to see, with an outcome positive or negative, and they go back to see not one single risk-factor, for instance, low FEV1, but a set of risk-factors, low FEV1, low DLCO, cardiac ischemia, elderly patients, so, the outcome is influenced by a multifactorial set of risk-factors. This is done in multivariate analyses. For doing so, if you're starting your career, you need to have a friend who is a clinical epidemiologist because this is not easily done. Multivariate analysis is not so simple as reading a book and then I'm publishing my multivariate analysis. So, my recommendation is if you have a good idea, go to the clinical epidemiology department in your hospital or call your friend who is an expert in that and ask him or the team to help you to design the study. Look at this title, the authors are very intelligently mixing up a prevalence study and a case-and-control study on a multivariate analysis. So, they are mixing up a prevalence study, a cohort analysis, and a multivariate analysis and they are reflecting it in the title of the study. A word of caution, try never to fish P values under 0.05 in your series of cases. If you have a set of variables in your retrospective analysis, never try to fish up P values. "Oh, H is correlated," or "DLCO or DNA mutations," or whatever because these kinds of maneuvers are always detected by the editor of the journal. Look at this example, I have hidden the names of the authors. The authors are investigating if non-intubated versus intubated anesthesia is effective on a series of outcomes. So, non-intubated cases are cases, and controls are intubated patients. These are not randomly assigned to a group, so, this is not a randomized trial, but is a case-and-control study. And the authors instead of studying one single outcome, for instance morbidity, are studying a set of outcomes, a multifactorial outcome. And they found that post-operative fasting time is the most significant modification in, I mean, post-operative fasting time is much lower in non-intubated patients with a P value under 0.001; while the other ones are, well, hardly significant. And they conclude that postoperative fasting time is significantly better, suggesting a more rapid recovery in non-intubated patients. If I am the editor of this paper, I go to the literature and I found that prolonged fasting time is not needed when using laryngeal mask, that is when the patient is not intubated. So, this conclusion is nonsense. What the authors did was trying to pick up some P under 0.05 values in their series and they concluded this, which is irrelevant. So, be very serious and discuss very well which are the outcomes of relevance in your series. And remember, ask your questions at the end of my presentations if you have one. Cohort studies. Cohort studies are expensive, time consuming, but the benefit is that, usually, unbiased and are more conclusive on association. In cohort studies, we have a nice hypothesis on etiology, select a population and in that population identify people with or without a risk-factor and then, we follow the patients up until the end of the series and then we measure the outcome and compare. So, we start with a population free of outcome, we found, in this population, patients with the risk-factor positive and negative and we follow the patients until the outcome is present or absent in the series. This is, maybe, the perfect example for that is the Framingham Heart study, where the authors tried for many years to identify risk-factors for cardiovascular diseases. In these kinds of studies, you're not measuring the odds-ratio, but the relative-risk which is measured in this way, as I'm showing to you in this slide. Of course, you can do it with your mobile phone or with a hand calculator and not many knowledges of mathematics are needed, but this is paramount: you need a good, a very good question to investigate. Finding the right question in your studies is paramount. I'm recommending to you reading this paper where the authors are citing a previous paper from a different journal and they define the criteria for a good research question. It should be feasible. For being feasible, you need an adequate number of subjects to be included in the study. If your practice is limited to a small area having 10 cases a year, probably, you cannot design a fantastic epidemiological study, but you can do something. You need to have the money or the resources and the topic

should be interesting, getting the answer which intrigues to the investigator and the community. For doing so, you need to read a lot on the internet. You need to go back to the internet, to Pac Med or whatever you want and find if this question is interesting to your community of specialists. It should be novel. In my personal experience, I found several times in my practice that the study I was designing was published two or three years ago. This is a problem of not reading enough medical literature. So, you must be sure that the topic is novel, it is ethical, it should be reviewed by the ethical review board in your institution and relevant. To be sure that it is relevant, my recommendation is that you commend the topic to your friends not to your competitors, maybe, for obvious reasons, but to your friends. Call Professor Bertolaccini, maybe, and say, "Hey, Luca, what do you think about that? Do you think it's interesting?" Or other friends in different centers and all that. So, let me conclude my talk in few words. There are two main types of epidemiological studies. Experimental and observational. These are aimed to investigate the causes, these are not. These are discovering just association, so, you never try to conclude on etiology. These studies are aimed to design good experimental studies. Second, randomized clinical trials are the kings in the evidence land, but they are very expensive and you need a very good training and experience in medical epidemiology. So, before being involved in this kind of design, try to get a good education in the topic. Case control are not the king, but the prime minister in the evidence land, but never compare pears and apples. For doing so, try to design your studies in matching cases and controls. Try to find a good research question which is feasible, interesting, novel, ethical and relevant and finally, what about P values under 0.05? This value is not the king in medical investigation because sometimes if you conclude, just because you are finding a P value under 0.05, you're immediately detected by the editor and your manuscript is rejected. So, questions, please make them interesting, novel, ethical, and relevant. Thank you very much for your attention.

Dr Bertolaccini: Thank you so much. Thank you so much. We are really proud to have this evening in the European School of Oncology, the Professor Varela and there is a relevant number of attendees this evening probably due to the argument and we have some questions. The first is, "If you get the chance, could you also talk about α-error and β-error or how the sample-size changes by this error, the power of the study?"

Dr Varela: Yeah, thank you very much for this question. This is not a talk on statistics. So, I didn't fix a talk on mathematics and on design and all that because that takes a lot of time, not just half an hour. Of course, the risk, when you're designing a study of clinical epidemiology you have several risks. One is accepting as a true conclusion what it is not true and the second one is not accepting as true what in fact is true. For doing so, at the beginning of the study, you must conduct a series of statistical or mathematical estimation and numbers to estimate the number of cases, the error you're accepting in your series of cases and so-and-so. But I think, this topic is rather a matter of a large discussion in a different talk. I can fix a talk, if I'm invited to do so, on this topic but not exactly at this time because it's quite a different topic. But in summary, my recommendation, when you are starting your career in medical, in clinical investigation, never try to do it alone. Never try to do it by yourself. Ask your friends who are experts in medical epidemiology to help you and, of course, you need to read, you need to study, or whatever, but when I'm talking to residents in my practice, I'm always trying to insist, "We are doctors, we are not mathematicians." So, our first job is treating patients. So, I apologize for not extending a lot in my answer but I don't think this is a talk on this topic.

Dr Bertolaccini: We have another question, sometimes, in your research, you find absolute opposite what has been reported in the literature, yet you can't find any errors in your research. So, how to approach such kinds of results?"

Dr Varela: That's a quite interesting question. And that happened to me many times in my, of course, I have much more papers rejected than accepted in my practice. When you go to a conclusion and you find in the literature something which is totally opposed to your conclusion, this happened many times, you must recognize in your manuscript that other different authors found completely contradictory results and you must honestly cite these authors and discuss the reasons for that. Sometimes, the problem is bad-design in your investigation. And if that is the problem, the only thing you can do is thinking twice on your investigation.

But if you're quite sure that you're right, the best you can do is trying to publish and honestly discussing the opposite results from different investigators. And also, if you're attending a meeting, hopefully, we'll be able to attend presential meetings next year, I pray God for that, try to find the author who published a different conclusion and discuss with him, because from these kinds of discussions, sometimes, the result is a fantastic new paper cooperating two teams with different point of view.

Dr Bertolaccini: Another question from the audience, for instance, could suggest a good title about this, "Breast conservative surgery versus mastectomy in locally advanced breast cancer patients." In your opinion, is it a good title?

Dr Varela: In my opinion, it is not because there're too many similar papers. What I'm using to do is deciding the title at the very end of the investigation. And we try different titles in the team. We are working together and I go to the rest of the guys and say, "Hey guys, what do you think about this title?" And some young people always say, "Ah, that's bullshit, I don't like it..." But to me, in this case, the best title would be, abstracting in one single sentence, "The results of your investigation", if you have found that conservative surgery is better, why not stating it clearly in 10 words, "Conservative surgery is equivalent to mastectomy in blah, blah blah?" And that's the title.

Dr Bertolaccini: Another question is, in your opinion, what is the right method for a young physician to start or to learn the medical writing, course, mentorship?"

Dr Varela: In my experience, I did a mistake at the beginning because I attended some statistical courses. I know nothing about mathematics. I was very bad at school in mathematics. So, I could understand nothing in these courses. I had a mess in my brain. I started to see the light when I read the book I was showing to you at the beginning. And after that, I was a student in a very well-organized course, not on statistics, but on clinical epidemiology. But I had, from the beginning, a little knowledge after reading the book. I used to read that book on the subway, when I was going to the hospital, back and forth. So, it's very simple to be read. So, my recommendation is, buy a good book, is not expensive, and start to read and when you have a little knowledge on that, you're taking notes on the book and taking your doubts and all that and then you should attend a small course. You don't need to have a PhD on medical epidemiology, just attending a course. Most societies, and of course, oncology societies in Europe and in the US and in Asia, in Africa are conducting courses and to my knowledge, most of them are fantastic courses.

Dr Bertolaccini: Thank you so much, Professor Varela. We have a lot of messages like this, "Thank you, Professor, for the excellent talk." "Thank you, Professor, for the clarity," and so on. And one is, "Thank you, Professor Varela for the excellent talk, as usual", and I agree because I have had the privilege to hear and to read Professor Varela in these years in our Congress of our societies, and this evening was a real honor for the European School of Oncology have the Professor Varela as a speaker. Thank you so much.

Dr Varela: Thank you, thank you very much. If someone in the audience is willing to send me an email with more questions, I'll be very, very happy answering. Thank you, Professor Bertolaccini and the European School of Oncology. It's been a great pleasure for me sharing this time with you, thank you.