Title

Pipeline: Ocular biostatistics: Proper use of proportions

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FOOTNOTES
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Disclosure:
Gary D. Novack PhD consults with numerous pharmaceutical and medical device firms.

We use proportions frequently in our daily lives. Achieving a score of 100% on any test needs no explanation – it means perfect –irrespective of whether it was 1 or 100 questions. However, achieving less than a perfect score, and how to report or interpret such results, is sometimes misleading. This gets even more complicated when comparing two treatments. In this article, I will give some examples, and a recommendation for all scientists in meaningful reporting.

Consider the roles in the television comedy series, Friends. They were Rachel, Phoebe, Chandler, Ross, Monica and Joey. The prevalence of "Rachels" is 17% (1/6). If the producers had added one more cast member, with the name of Rachel, then the prevalence of "Rachels" would be 28% (2/7). This would be an increase of 11% - a 64% increase. You can imagine that if you heard "64% increase" and did not know that it was just one person, you might reach very different conclusions (Figure 1).

Consider a medical epidemiological example. Current lung cancer screening guidelines exclude smokers who are more than 15 years since quitting (YSQ). In a comprehensive paper, Tindle et al used data from the Framingham Heart Studies with respect to lifetime smoking history and risk of lung cancer. Working with a very large population (~9,000 patients with over 75,000 person-examinations over decades), they concluded that "Among heavy former smokers, lung cancer risk drops within five years since quitting (YSQ) relative to continuing smokers, yet it remains more than threefold higher than never smokers after 25 YSQ." Then went further to suggest that the criterion of "15 YSQ" is not adequate. The authors provided complete details on the number of patients examined, the number of cases, and the hazard ratios for various patient populations.[1] While one could quibble about exactly which ratio to use, given the major impact of smoking (even with cessation) on later lung cancers – up to 12-fold difference between current heavy smokers and those who have never smoked – fine statistical issues probably do not matter. That is, the treatment effect is so large it is clear in any data presentation (Figure 2).

Consider one of the pivotal clinical studies for the Comirnaty® COVID-19 vaccine, the occurrence of COVID was 0.39% (77/19,993) in the treated group compared to 4.1% (833/20,118) in the placebo group. This gave a vaccine efficacy of 91.1% (95% confidence interval of 88.8 – 93.1). One could say that there was a 10-fold (1000%) difference in infection rates. Alternatively, one could say for 96% of patients, a vaccine is not needed.
https://www.fda.gov/media/151733/download

Now consider an ophthalmology example. In the Ocular Hypertension Treatment Study (OHTS), Kass et al randomized over 1600 patients with ocular hypertension to topical ocular hypertensive treatment or no treatment. At 5 years, the cumulative adjusted probability of developing glaucoma was 4.4% (30/690) in the medication group and 9.5% (64/673) in the observation group (hazard ratio, 0.40; 95% confidence interval, 0.27-0.59; P<.0001).[2] These results have been cited by many people in many different ways in the over 20 years since publication. Some say "it's only a 5% difference – while others say "it's a doubling of risk" (Figure 3). As with the "Friends" example, the way in which these data are stated conveys very different interpretations.

Finally, consider an example in the treatment of dry eye disease (DED). There are 3 approved topical ocular cyclosporine products in the U.S. The package inserts for each of them may be found at https://dailymed.nlm.nih.gov/dailymed/. The primary outcome measure for each product was patients who experienced an increase in Schirmer wetting score of 10 mm or more. Each product had two or more double-masked, vehicle-controlled studies which I have combined together for the purposes of this illustration only. For Restasis®, the primary outcome was achieved in 15% (~90/600) patients in the active group vs. 5% (~30/600) patients in the vehicle group for a treatment effect of ~10%. For Cequa®, the primary outcome was achieved in 17% (88/523) patients in the active group vs. 9% (47/525) in the vehicle group for a treatment effect of ~8%. For Vevye®, the primary outcome was achieved in 11% (49/460) of patients in the active group and 6% (27/446) of patients in the vehicle group, for a treatment effect of 5%. One way to view this data is that each cyclosporine product is effective in about 4 to 10% more patients than vehicle. Another is to view that 85% to 91% of patients will not benefit from cyclosporine (Figure 4).

In summary, if the treatment effect was as great as the influence of smoking on lung cancer, or as trivial as "adding a Rachel" to the cast of Friends, percentages alone would be enough. However, for treatments of ocular surface disease, where the effects, especially compared to vehicle, are relatively small and variable, we need to clearly define numerator and denominator when giving percentages to avoid inappropriate conclusions.

References

1. Tindle HA, Stevenson Duncan M, Greevy RA, et al. Lifetime Smoking History and Risk of Lung Cancer: Results From the Framingham Heart Study. *J Natl Cancer Inst* 2018;110 (11):1201-1207.
2. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120 (6):701-13; discussion 829-30.

News regarding ocular disease

- Alcon announced results from its COMET-2 and COMET-3 Phase 3 trials of its topical dry eye treatment, AR-15512 (January 2024).
- Aldeyra entered into an option agreement with AbbVie for a license to develop and commercialize reproxalap (November 2023).
- Azura announced results from its Phase 2 trial of AZR-MD-001 in patients with contact lens discomfort with meibomian gland disease (December 2023).

Figure Legends:

FIGURE 1: EXAMPLE OF ADDITION OF ONE ADDITIONAL "FRIEND" NAMED "RACHEL" TO THE FRIENDS CAST. SHOWN ARE THE NUMBER OF CAST MEMBERS, PERCENT AND CHANGE IN PERCENT OF "RACHELS" IN THE CAST

FIGURE 2: EXAMPLE OF THE INFLUENCE OF FORMER SMOKING ON LUNG CANCER RISK. SHOWN ARE THE NUMBER OF PATIENTS (LOG SCALE), THE RATE PER 1,000 PATIENTS, AND THE TREATMENT EFFECT

FIGURE 3: EXAMPLE OF THE OCULAR HYPERTENSION TREATMENT STUDY (OHTS). SHOWN ARE THE NUMBER OF PATIENTS BY TREATMENT GROUP (TREATED OR NO TREATMENT), PERCENT OF PATIENTS BY TREATMENT GROUP, TREATMENT EFFECT, AND PROPORTIONAL TREATMENT EFFECT

FIGURE 4: EXAMPLE OF TOPICAL OCULAR CYCLOSPORINE PRODUCTS APPROVED IN THE U.S. SHOWN ARE THE NUMBER OF PATIENTS, PROPORTION OF PATIENTS, AND PROPORTIONAL TREATMENT EFFECT FOR ACTIVE-1 (RESTASIS®), ACTIVE-2 (CEQUA®) AND ACTIVE-3 (VEVYE®). DATA FROM PACKAGE INSERTS AND SUMMARY BASIS OF APPROVAL

Figure 1: Example of addition of one additional "Friend" named "Rachel" to the Friends cast. Shown are the number of cast members, percent and change in percent of "Rachels" in the cast

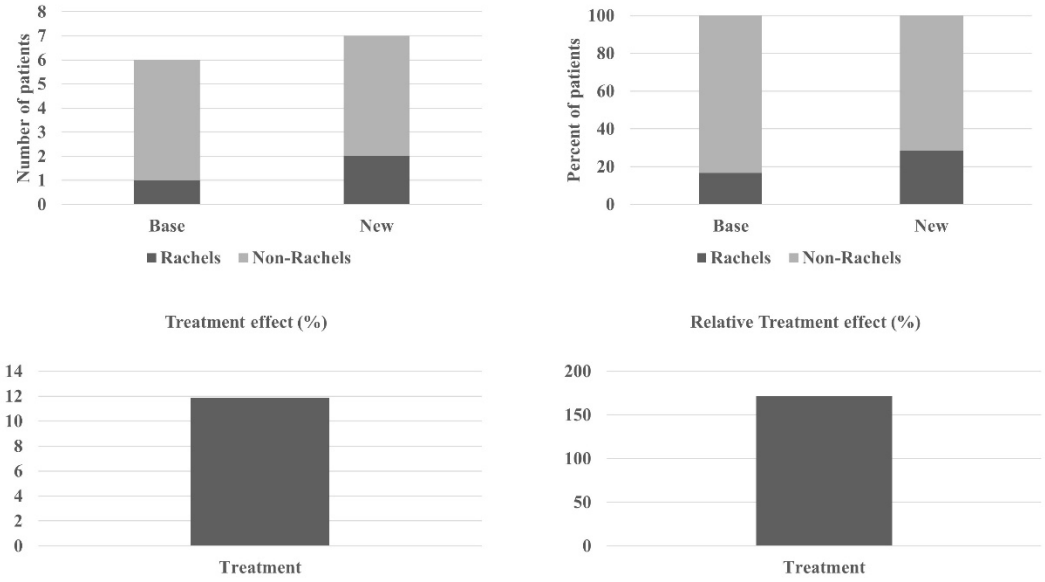

Figure 2: Example of the influence of former smoking on lung cancer risk. Shown are the number of patients (log scale), the rate per 1,000 patients, and the treatment effect

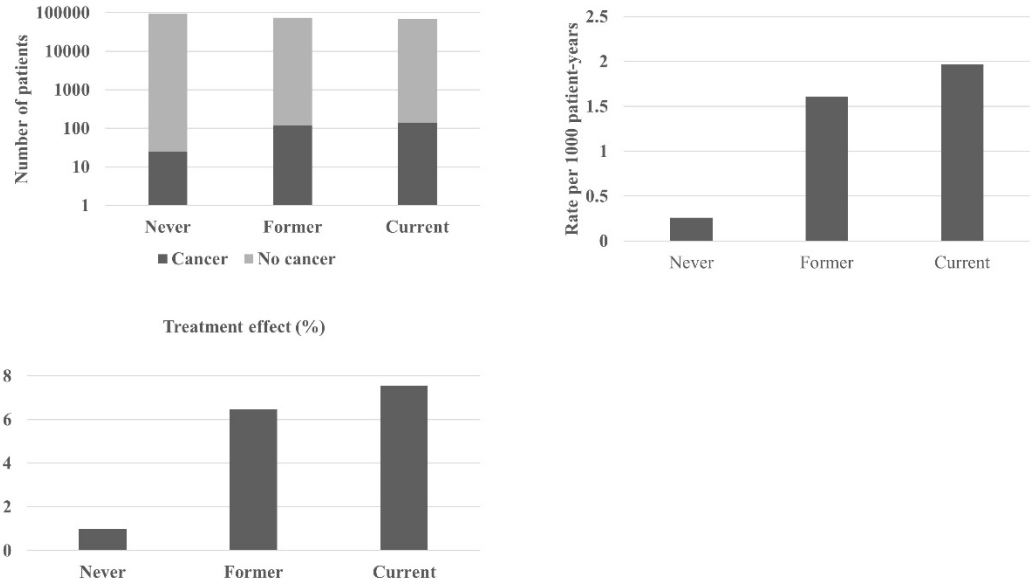

Figure 3: Example of the Ocular Hypertension Treatment Study (OHTS). Shown are the number of patients by treatment group (treated or no treatment), percent of patients by treatment group, treatment effect, and proportional treatment effect

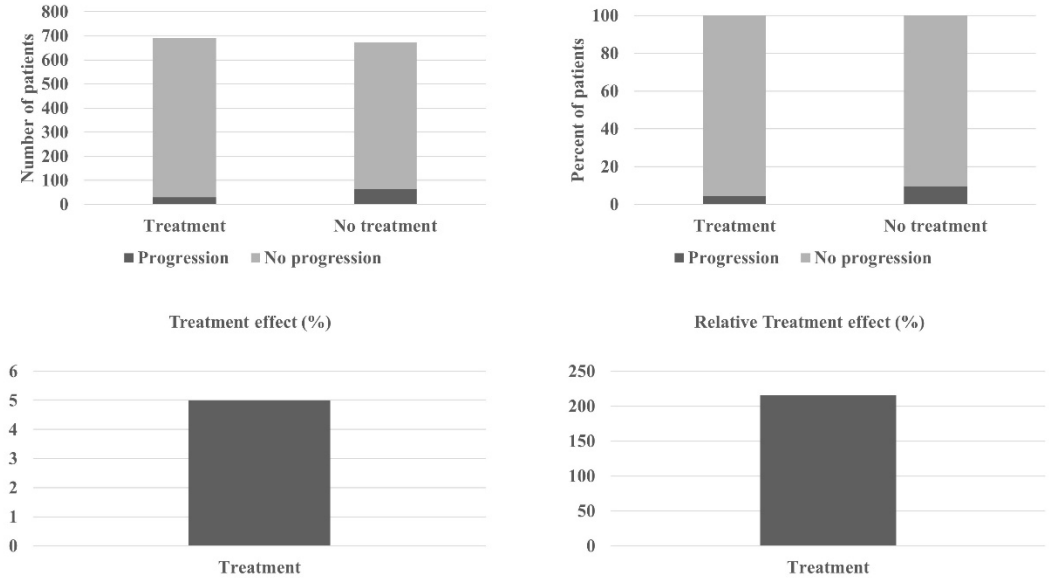

Figure 4: Example of topical ocular cyclosporine products approved in the U.S. Shown are the number of patients, proportion of patients, and proportional treatment effect for Active-1 (Restasis®), Active-2 (Cequa®) and Active-3 (Vevye®). Data from package inserts and summary basis of approval