

Clinical Impact: When to Schedule for the Upcoming Screening Exam?

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Opinion

I was attending a local conference at Louisville, KY last October, and made a poster presentation in the hall with a group of researchers. One visitor stopped by and asked me a question after I introduced the topic (i.e., over diagnosis and long term outcomes in lung cancer screening). He asked what the clinical impact of your study was. That is, could this research be translated directly into something that physicians really care about and are useful to them? Huh, that is a good question. In fact, translational research should have some impact in real life and NIH reviewers do evaluate clinical impact when they read and grade grant applications. And that inspired me to work on this topic: when to schedule the next screening exams for asymptomatic people who just get a negative result?

Here is the background of this problem: we assume that all clinical cancer will develop through three states: disease free, preclinical, and clinical state; where the disease-free state means that either there is no disease or the disease cannot be detected by screening techniques; the preclinical state refers to an asymptomatic individual unknowingly has the disease that a screening exam can detect; and finally the clinical state refers that the disease has showed clinical symptoms. Current model assumes that there is no reverse of the process, that is, people in the preclinical state will not move back to the disease free state, but he/she can either stay in the preclinical state or move to the clinical state. The progressive model describes the natural history of tumor development.

Now for an individual who has taken screening exams in the past with negative results (including both true negative and false negative), and who is superficially healthy now, when to schedule his/her next screening exam? Using breast cancer screening as an example: Should she come back for the exam after 6 months, 12 months or longer? What would be her best choice? Diagnostic radiologists face this problem almost every day: how to provide informed and satisfying advice to a patient in this scenario?

Some research work has been done in optimal scheduling for screenings before. Zelen [1] developed a utility function to find the optimal scheduling for the next $(n + 1)$ exams. This is equivalent to a fixed budget which allows only $(n + 1)$ examinations." - quoted from Zelen. The utility function needs to assign different weights to cases diagnosed by the first exam, cases diagnosed at subsequent exams, and the interval cases. The optimal spacing of the exams is to find a sequence of time that maximizes the utility function. Zelen [1] found that for the optimal intervals to be equally spaced, the screening sensitivity must be 1, which cannot be achieved in reality. Another issue is the choice of the weights used in the utility function, which is more subjective. Lee and Zelen [2] developed a threshold method and a schedule sensitivity method. Their threshold method calculates the

probability of being in the preclinical state, and exams are scheduled whenever this probability reaches the same value as that at age 50 (which is 0.0018 in their simulation). They found that the screening interval is getting smaller as people aging. The schedule sensitivity is the ratio of the expected number of diagnosed cases on scheduled exams to the expected number of the total cancer cases. Hence schedule sensitivity will increase if more screenings would be scheduled in a fixed time interval. Again, costs or weights were involved in their schedule sensitivity. There are other papers, such as Parmigiani [3,4] Parmigiani et.al. [5], on optimal scheduling. All these researches use some kind of utility functions that involve cost or weight. Their contributions are on the optimal scheduling for $(n + 1)$ exams as a group, but not focusing on the next upcoming exam for individuals.

A totally different approach is proposed here handle the scheduling of the next upcoming screening. There is not any weight, cost, or utility functions involved. The focus is not on the $(n + 1)$ exams; instead, the focus will be on the next coming exam for an individual based on her/his screening history and current age. More specifically, the conditional probability of incidence before the next exam, given one's screening history and age will be derived. Then the next screening interval shall be chosen, such that this probability will be limited by some preselected small value, say 10%, 5% or less. Hence, with 90% or more chance, a woman will not become a clinical incidence case of breast cancer before her next scheduled exam. The conditional lead time distribution, given that one would be diagnosed with cancer at the next screening exam can also be derived. This could provide individuals (based on their screening history and age) some predictive information regarding how early the diagnosis could be if they would develop cancer and follow this schedule. The research may provide a theoretical and practical basis to guide individuals or physicians to make informed decision in screening exam. Specifically, the research may solve the problems of when cancer screening should be performed for different individuals with different risk factors in the near future.

References

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