Do Never Smokers with Lung Cancer Have a Different Disease?

Just a few years ago, the only distinction in the field of lung cancer that meant anything was small cell vs. non-small cell. The different types of non-small cell, like adenocarcinoma vs. squamous cell vs. large cell, were of little interest and didn’t change management (only a very recent development). And although we often asked about smoking history, the answer never changed our treatment plan. Only in the last few years have we come to recognize that we will do better as “splitters” than as “lumpers”, by tailoring our treatment recommendations to the clinical and molecular feature of one particular patient and tumor at a time, rather than using a one size fits all approach.

First, some definitions. Although there is a little variation, most of the lung cancer research community has come around to a definition of a “never-smoker” as less than 100 cigarettes in a lifetime. A “former smoker” is more than that and has quit smoking for at least a year. A “current smoker” is anyone else, so less than a year after quitting, a patient is still considered a current smoker.

And among patients diagnosed with lung cancer, what is the breakdown by smoking history? As shown in the figure below, the majority of people diagnosed with lung cancer these days are not currently smoking. Just a little more than a third are current smokers, half are former smokers, and about 10-15% never smoked.

But it really varies where you are. In California and up in Seattle where I practice, probably 25-30% of my patients are never-smokers. And I very rarely see small cell lung cancer, which is almost always associated with smoking, and usually a pretty significant amount over a long time.

I’m talking about North American numbers, because many Asian series show that they’re seeing 30-50% of their lung cancer patients as never-smokers. It’s amazing, but it’s that way in study after study coming out of Japan, China, and Korea.

Several studies have compared groups of smokers and non-smokers and reported that the never-smokers tended to do better and live longer, stage for stage, than current or former smokers. There are a mix of results on this, though, and it still wouldn’t clearly explain whether this occurred because never-smokers responded better to treatment or had fewer other...
medical problems like emphysema or heart disease that are also smoking-induced.

So a few general principles in terms of the never-smoker lung cancer population. Unlike the general lung cancer population, which is predominantly male, the never-smoker lung cancer population is about 60-70% female — we don’t understand why yet, but it’s debated whether women are more likely to develop lung cancer with a lower extent of tobacco exposure. And I already mentioned that never-smokers almost never have small cell lung cancer. And while general NSCLC consists of 40-50% adenocarcinomas (including about 3-4% bronchioalveolar carcinoma, or BAC), 25-30% squamous cell carcinomas, 10-15% large cell lung cancer, and a small percentage of large cell “neuroendocrine” tumors, the never-smokers are overwhelmingly adenocarcinomas, with or without BAC features. About 1/3 of BAC patients have never-smoked.

The causes are really not well known. Passive smoke is certainly part of the problem, estimated as responsible for perhaps a quarter of cases, but it’s extremely hard to measure, so we really don’t know. Radon is estimated to be responsible for some cases as well. Occupational exposure to toxins can occasionally be a cause. There has been speculation that some cooking oils at a high temperature, such as used in a wok, may release toxic fumes that could be responsible for some of the high frequency of cases in Asian women, but that’s more of a theory than a proven conclusion. In many cases, it’s just a random event that we can’t explain.

The studies of tumors from never-smokers generally have far fewer mutations than are seen in the tumors of smokers, so it seems that they are generally driven by just a few critical mutations rather than an accumulation of a much larger number over time. Smokers tend to have many mutations in their tumor and also many in the normal tissue around the tumor, so it appears the tumor just accumulates an extra “straw that broke the camel’s back” beyond the background “field defect” from chronic tobacco exposure that affects the rest of the lungs. I’ve included a figure showing the gene expression patterns of a small number of smoker tumors vs. never-smoker tumors. The individual genes aren’t important, but you can see clear differences in the pattern of genes turned on and off in the lung tumors of smokers and never-smokers.

Some of these genes may have particular implications about targeted therapy options that are currently available. I'll describe the treatment implications of smoking status in my next post.
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