



**Never-Smokers with Lung Cancer:
A Compelling Story for a Distinct Disease**
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Hello and welcome to the GRACE video presentation on the distinct features of the lung cancer seen among never-smokers. My name is Dr. Jack West and I'm a medical oncologist and the Medical Director of the Thoracic Oncology Program at Swedish Cancer Institute in Seattle Washington. I also serve as the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

A transcript as well as a PDF file with copies of figures associated with this program are available at www.cancergrace.org/GRACEcasts.

This video presentation is in loving memory of Michael Zhao, who fought not only for himself but participated in research in part to help others fighting this disease.

The information provided here includes my own views and they are not necessarily those of the Global Resource for Advancing Cancer Education or those of Swedish Cancer Institute. The contents of this program do not constitute medical advice and they are intended to supplement but not replace input from an individual's patient medical team.

As we begin the discussion of never-smokers with lung cancer, we need to clarify the generally accepted definitions of smoking status within the field of lung cancer. Never-smokers are those who have smoked fewer than 100 cigarettes in their lifetime. Ex-smokers are those who quit at least before diagnosis, and current smokers are those patients who continue to smoke or quit within less than a year of diagnosis.

About half of new lung cancer patients are ex-smokers, while never-smokers comprise about 10-15% of most lung cancer series in North America. Though obviously a minority of the general lung cancer population, never-smokers with lung cancer account twenty thousand or more new cases in the US each year, which would rank it among the top ten most common cancers even on its own.

In addition, studies from Asia tend to see up to a third of patients as never-smokers, higher numbers than seen in North America. Other distinctive aspects of lung cancer in never-smokers include that it is very most commonly an adenocarcinoma, and quite often specifically the bronchioloalveolar carcinoma, or BAC, subtype. Lung cancer among never-smokers disproportionately affects women compared with men on both continents.

In trying to discern the underlying cause of lung cancer in never-smokers, second-hand smoke exposure, radon, possible occupational toxin, and pollution have all been implicated, but this remains a largely unexplained medical question.

Though there is still a great deal to learn about the biology of lung tumors in never-smokers vs. those in smokers, the available genetic evidence clearly and consistently indicates that the lung tumors in never-smokers are genetically relatively simple compared to those of smokers, and they appear to be very different from the surrounding normal lung tissue. In contrast, the lung cancers of smokers have a larger number of mutations and are genetically similar to the surrounding lung tissue, which tends to have genetic features different from the non-cancer lung tissue of never-smokers. Overall, this work suggests that the lung cancers of never-smokers may be more of a random key hit compared with those arising in smokers, which appear to be more of a cumulative effect of many genetic abnormalities seen throughout their lung tissue.

Some studies have demonstrated that never-smokers have a superior survival compared with current or ex-smokers. One large review of the experience of lung cancer patients over a four year period from Henry Ford Hospital in Detroit, where only 8% of patients were never-smokers. This review showed that survival was significantly worse in current or ex-smokers, though smoking was also associated with a greater frequency of other medical problems, worse nutrition, and overall less treatment. Nevertheless, when these factors were isolated in a separate analysis for these related variables, there was still a significantly better survival seen among never-smokers.

Similar conclusions have been seen at Moffitt Cancer Center in Tampa, where they looked at 654 patients with adenocarcinomas. Within this population, never-smokers were disproportionately women, more likely to have the BAC subtype of lung cancer, and had a significantly better long-term survival, even when the investigators took into account related variables and isolated the difference of smoking status.

We've also seen better survival among never-smokers specifically in the setting of advanced non-small cell lung cancer. In the trial comparing cisplatin/gemcitabine, also known as gemzar, to cisplatin/pemetrexed, also known as alimta, both treatment groups demonstrated a 5-6 month longer median overall survival in never-smokers, who comprised about 15% of the patients enrolled in this international trial.

But in truth, much of the reason we've focused on never-smokers over the last few years stems from the observation that never-smokers were particularly likely to respond to the oral inhibitors of the epidermal growth factor receptor, or EGFR. For instance, in the retrospective review of 139 patients treated with gefitinib, also known as Iressa, at Memorial Sloan Kettering Cancer Center in New York over a five year period, never-smoking status was among the strongest discriminators of likelihood of significant response, and it was one of two variables that emerged as significantly predictive in a careful multivariate analysis that separated associations with overlapping variables.

The importance of smoking status and particular benefit in never-smokers has also held up in larger studies. The BR.21 trial that tested the EGFR inhibitor erlotinib, also

known as Tarceva, versus placebo in previously treated patients with advanced non-small cell lung cancer, showed a significant improvement in median overall survival by a couple of months, as well as a significant improvement in progression-free survival. When results were evaluated by patient subgroups, never-smokers got more benefit than any other subgroup, more than doubling survival with Tarceva compared with placebo, as shown in the very striking separation of curves on the left, a far greater effect than that seen among current or former smokers, represented in the curves on the right.

The same picture emerges from a very similar, larger trial done with Iressa. Unlike the BR.21 trial with Tarceva, the ISEL trial, for Iressa Study Evaluation in Lung Cancer, did not show a significant difference in survival for the general trial population, but there was a nearly three month improvement in median overall survival with Iressa among the never-smokers on the trial, as shown in the separating curves on the bottom left. In contrast, there was no evidence of improvement among the current or former smokers on this trial.

In a trial that I led of Iressa in patients with advanced bronchioloalveolar carcinoma, never-smokers had a significantly longer survival that nearly doubled that seen in smokers on this study. In a similar trial of Tarceva in advanced BAC, there was a more than doubling of response rate for never-smokers compared with current or ex-smokers.

Another trial approach in which never-smokers have appeared to receive particular benefit has been the combination of oral EGFR inhibitor therapy with standard chemotherapy. Four different trials that compared first line doublet chemo to chemo with concurrent EGFR inhibitor therapy were quite clearly negative for a survival benefit from adding Iressa or Tarceva, including this one, called TRIBUTE, that added tarceva or placebo to up to six cycles of carboplatin and paclitaxel, also known as Taxol.

Nevertheless, this negative trial was positive for one subset of patients, and that was never-smokers, in whom there was a significant improvement in both overall survival, on top, and progression-free survival, on the bottom. This result is a leading reason why some oncologists recommend concurrent chemo and Tarceva for some patients, particularly never-smokers, though I would highlight that the curves really separate only about 6 months into the trial, when the 6 cycles of chemo are completed. I believe that never-smokers did well with this approach despite and not because of the concurrent chemotherapy. We can hope to get some information about this question from a still ongoing trial for never-smokers or light former-smokers, who are being randomized to chemo with Tarceva or Tarceva alone.

To summarize, never-smokers account for over 20,000 new cases of lung cancer in the US each year, and have several features that are distinctive compared with the lung cancer arising in current or former smokers. Never-smokers with lung cancer are disproportionately women, are particularly common in Asia, all for reasons we don't yet understand. The lung cancer in never-smokers tends to be an adenocarcinoma, and up to a third of patients with BAC are never-smokers. These tumors in never-smokers are overall less genetically complex. Perhaps related to this, they may be more responsive to our treatments, as survival is consistently longer in never-smokers. This is seen in a

range of trials, but it has been most pronounced in studies of oral EGFR inhibitors. In positive trials, never-smokers are the subset with the greatest benefit, while in overall negative trials, never-smokers emerge as a subset in whom a benefit can still be seen. These trials are with Tarceva or Iressa, alone or in combination with chemotherapy.

There is still a great deal we need to learn about why lung cancer emerges in never-smokers and whether there are particularly effective approaches to pursue in these patients, but the field has exploded as a field of research within the last few years, and never-smokers are being more carefully studied as defined subsets in larger trials, as well as in specific trials dedicated to never-smokers. Among the most important questions to address is whether the clinical variable of smoking status is really the most relevant variable or that being a never-smoker is correlated with one or more molecular variables that are really the key. We'll cover this question as a separate presentation.

You can find additional information on several of these topics within the subject archives at the web address www.cancergrace.org/lung. Members of GRACE can also leave comments and questions about this presentation at the web address below.

Thank you for your interest.