Inherited T790M EGFR Mutation and Lung Cancer Risk

H. Jack West, MD
T790M Mutation in the EGFR Gene

• T790M is a mutation on a portion of the gene for the epidermal growth factor receptor (EGFR) that drives a minority of lung cancers.

• Specifically, the T790M mutation, which is on a portion of the gene called exon 20, is associated with resistance to oral tyrosine kinase inhibitors (TKIs) of the EGFR protein, such as Tarceva (erlotinib), Iressa (gefitinib), and Gilotrif (afatinib).

• It is the most common cause of acquired resistance to EGFR TKIs (~60% of cases).
T790M: Acquired vs. *de novo* (from the beginning) Mutations

- In the vast majority of patients with a T790M mutation, it is a *somatic* mutation. This means that it developed in only a subset of body cells. The alternative is a *germline* mutation, passed on from egg or sperm of a parent, and which is present in ALL of the body cells.

**Somatic Mutation**
- In non-germline tissues
- Cannot be inherited
- Mutation is in tumor only (for example, breast)

**Germline Mutation**
- Present in egg or sperm
- Can be inherited
- Cause familiar cancer syndrome
- Mutation in egg or sperm
- All cells affected in offspring

**HERITABLE**
Inherited T790M Mutations

• A small minority of people with lung cancer have been found to have a de novo, germline T790M mutation. How small? The medical literature includes reports of 15 patients throughout the world prior to new report (April, 2014) in the Journal of Thoracic Oncology:

  Hereditary Lung Cancer Syndrome Targets Never Smokers with Germline EGFR Gene T790M Mutations

  Adi Gazdar, MD,*† Linda Robinson, MS,‡ Dwight Oliver, MD,† Chao Xing, PhD,§ William D. Travis, MD,∥ Junichi Soh, MD,¶ Shinichi Toyooka, MD,¶ Lori Watumull, MD,# Yang Xie, PhD,** Kemp Kernstine, MD,†† and Joan H. Schiller, MD,‡‡

• This report described a case of a 29 year-old woman treated at the University of Texas-Southwestern with lung adenocarcinoma and minimal smoking history, found to have a T790M mutation at diagnosis, who underwent workup of her family that included 5 generations and identified 14 individual carriers of a germline T790M mutation.

• The group studied these 14 plus 15 in the literature (=29 total), of whom 19 have had lung cancer.
Features of T790M-Associated Cancers, and Risk of Developing Lung Cancer

• Mutations are dominant (one copy out of two genes in each cell is enough to lead to increased cancer risk).

• Cancers were more common in women, predominantly adenocarcinomas, median age 63 (the 29 year-old subject of the UT-SW study was the youngest with lung cancer), and most (73%) had another EGFR mutation. T790M on its own is a weak driver of cancer, but it seems to accelerate risk when another mutation (such as an activating EGFR mutation) is present.

• Among carriers of the germline mutation, lifetime risk of developing lung cancer is estimated at 31%, or just under 1 in 3.
Implications for Screening and Concern about Familial Lung Cancer Syndromes

• However, most people with lung cancer, including never-smokers, don’t have an inherited T790M mutation. Risk of having an inherited T790M mutation if someone without known lung cancer is estimated at 1 in 7500.

• This means that the risk of carrying such a gene if you haven’t been diagnosed with lung cancer is 3-fold lower than the risk of having a fatal fall in the bathtub and shouldn’t be considered a major public health risk.
Screening for Carriers of an Inherited T790M Mutation

- On the other hand, for those with an inherited T790M mutation, if identified working back from someone with lung cancer, the risk of developing a cancer over a lifetime is in the range of 1 in 3.
- Though there is no formal screening recommendation, that level of risk certainly warrants early and regular chest CT screening.
General Conclusions

• Inherited T790M EGFR mutations are likely a very rare cause of lung cancer. However, we are likely to detect them more and more affected families as we do routine screening for mutations in newly diagnosed patients with lung cancer.

• We should expect to learn much more about these inherited mutations as we work backward from identified patients with a T790M mutation at the time of initial diagnosis, especially if they have a family history of lung cancer.

• Chest CT screening of the rare person identified as having an inherited T790M mutation makes very good sense.

• Though an important finding, inherited T790M is a small piece of a much larger puzzle.
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