Null Results in Brief

EGFR Somatic Mutations in Lung Tumors: Radon Exposure and Passive Smoking in Former- and Never-Smoking U.S. Women

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Abstract

Background: Patients with lung cancer with mutations in EGFR receptor (EGFR) tyrosine kinase have improved prognosis when treated with EGFR inhibitors. We hypothesized that EGFR mutations may be related to residential radon or passive tobacco smoke.

Methods: This hypothesis was investigated by analyzing EGFR mutations in 70 lung tumors from a population of never and long-term former female smokers from Missouri with detailed exposure assessments. The relationship with passive smoking was also examined in never-smoking female lung cancer cases from the Mayo clinic.

Results: Overall, the frequency of EGFR mutation was 41% [95% confidence interval (CI), 32%–49%]. Neither radon nor passive-smoking exposure was consistently associated with EGFR mutations in lung tumors.

Conclusions: The results suggest that EGFR mutations are common in female, never-smoking lung cancer cases from the United States, and EGFR mutations are unlikely due to exposure to radon or passive smoking.

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Introduction

Among never-smokers, lung cancer is the seventh leading cause of cancer death. A large proportion of lung cancer in never-smokers remains unexplained by established environmental risk factors. However, radon and passive smoke exposure were associated with lung cancer in never-smokers in several studies (for review, see ref. 1).

Lung cancer has a poor prognosis overall, but small-molecule inhibitors of EGF receptor (EGFR) result in improved survival in some patients. Therapeutic response correlates with somatic mutations in the EGFR gene. Those mutations are inversely correlated with cigarette smoking and more frequently observed in never-smokers (for review, see ref. 2). We investigated the possibility that residential radon or passive smoking were associated with the presence of EGFR mutations in lung tumors in 2 populations of female never and long-term former smokers.

Methods

Study populations

The Missouri Women’s Health Study case series included Caucasian lung cancer cases nested within a case-control study of never- and former-smoking women (3, 4). Patients with lung cancer from the Mayo Clinic were described previously (5). Cases were limited to Caucasian women to ensure comparability with the Missouri study.

EGFR mutation analysis

Missouri women. DNA previously isolated from microdissected tumor samples (4), available from 105 of 132 samples, was used for EGFR mutation analysis in the Laboratory of Human Carcinogenesis. Because of evaporation, the majority of DNA samples (74% or 78 of 105) were reconstituted using 10 µL of Tris-EDTA buffer (pH 7.5). PCR amplification was conducted as a 50 µL reaction including 2 µL DNA stock solution, 1.25 U of Native Pfu DNA polymerase (Stratagene), 1 × Pfu buffer, 300 nmol/L forward and reverse primers for either exon 19 or exon 21

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Note: Work was conducted when M. Taga and N. Hagiwara were in the Laboratory of Human Carcinogenesis.

M. Taga and L.E. Mechanic contributed equally to this work and conducted the analyses of EGFR mutations.

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Table 1. EGFR gene mutations in never- and former-smoking patients with lung cancer

<table>
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<tr>
<th>Patient ID</th>
<th>Histology</th>
<th>EGFR exon</th>
<th>Mutation type</th>
<th>Codon(s)</th>
<th>Nucleotide change</th>
<th>Amino acid change</th>
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(Continued on the following page)
of EGFR; primers were identical to those reported previously (6). Amplification was conducted using the following conditions: 95°C for 5 minutes followed by 40 cycles of 96°C for 45 seconds, 58°C for 1 minute, and 72°C for 1 minute; a terminal extension cycle of 5 minutes at 72°C was included. If initial PCR reactions failed to amplify, a second PCR amplification reaction was carried out using 5 μL of a 1:10 dilution of the PCR reaction mixture. Samples that failed the first series of amplifications were re-amplified using a second aliquot of genomic DNA. Overall, 32 (30%) of 105 genomic samples failed to amplify. DNA sequencing was conducted as per manufacturer’s instructions on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems) by NCI DNA MiniCore Facility in the Laboratory of Human Carcinogenesis. Results were similar when they were considered mutant (data not shown).

Never-smokers were defined as persons who had either smoked <100 cigarettes or did not use any tobacco products during their lifetimes. To examine association of any exposure to passive smoking in the Missouri study, categories of exposure (<21, 21–52, and >52 pack-years) were combined and compared with 0 pack-years. Former-smokers in the Missouri study abstained from tobacco for at least 15 years before interview (3). In the Mayo Clinic study, passive smoke dosimetry included both adult and/or in childhood exposures. Data analysis was conducted by SAS version 9.1 (SAS Institute Inc.) using 2-sided tests.

### Mayo clinic

EGFR mutations were analyzed at the Mayo Clinic as part of oncogene mutation screening using the OncoCarta Panel v1.0 (Sequenom) on the Sequenom MassArray Genetic Analysis platform following manufacturer’s protocol. Data analysis was conducted using MassArray Typer Analyzer 4.0 software (Sequenom). Performance of the assay was evaluated against a panel of lung tumor samples and cell lines with previously identified mutations. EGFR gene mutation data were available for all 73 cases from the Mayo clinic study.

### Statistical analysis

Samples with incomplete sequencing data for EGFR (e.g., failed amplification at one or more exons) were considered missing. The Mayo Clinic study had mutation data on additional EGFR exons compared with the Missouri study. Cases with mutations in exons other than 19 and 21 were considered wild-type for EGFR (N = 3).

Results were similar when they were considered mutant (data not shown). Never-smokers were defined as persons who had either smoked <100 cigarettes or did not use any tobacco products during their lifetimes. To examine association of any exposure to passive smoking in the Missouri study, categories of exposure (<21, 21–52, and >52 pack-years) were combined and compared with 0 pack-years. Former-smokers in the Missouri study abstained from tobacco for at least 15 years before interview (3). In the Mayo Clinic study, passive smoke dosimetry included both adult and/or in childhood exposures. Data analysis was conducted by SAS version 9.1 (SAS Institute Inc.) using 2-sided tests in the Laboratory of Human Carcinogenesis.

### Results

Twenty-four of the Missouri cases [34%; 95% confidence interval (CI), 23%–47%] and 34 of the Mayo clinic cases (47%; 95% CI, 35%–59%) had mutations detected in exons 19 or 21 of EGFR (Table 1). Overall, the mutation frequency was 41% (95% CI, 32%–49.0%).

While there was a difference in the quartiles of radon exposure associated with EGFR mutation (P = 0.01), this was not significant when exposure was dichotomized at the median (P = 0.14; Fisher exact test), and no difference was observed when considering radon as a continuous measure (P = 0.16) and there was no evidence for a dose–response relationship with radon exposure (Table 2).

In the Missouri Women’s Health Study cases, there was an inverse association of EGFR mutations with any exposure to passive smoke, but no clear dose–response relationship was observed with passive-smoke exposure quantified in pack-years. In the Mayo Clinic population,
no association was observed between \textit{EGFR} mutations and adult exposure, childhood exposure, or any exposure to passive smoke (Table 2).

\textbf{Discussion}

Our data do not support the hypothesis that radon exposure contributes to mutations in \textit{EGFR}. The mutation frequency appeared elevated at low-dose exposure and diminished at higher exposure levels, but we noticed a similar trend with \textit{TP53} mutations (4). The relationship of radon with lung cancer risk is thought to be linear (1), so our inverse trend between radon dose and \textit{EGFR} mutations probably occurred by chance.

We observed an inverse association of passive-smoke exposure with \textit{EGFR} mutations in lung tumors in the Missouri study, but this finding failed to replicate in

\begin{table}
\centering
\caption{Association of \textit{EGFR} mutations with patient characteristics}
\begin{tabular}{llllll}
\hline
 & \textit{Missouri women (EGFR)} & & & \textit{Mayo Clinic study (EGFR)} & \\
 & \text{\(- Mutation\)} & \text{\(+ Mutation\)} & \text{\(- Mutation\)} & \text{\(+ Mutation\)}
\hline
\text{Histologic subtype} & & & & \\
Adenocarcinoma & 34 (74) & 19 (80) & 0.98 & 28 (72) & 29 (85) & 0.28 \\
Bronchioalveolar carcinoma & 4 (9) & 2 (8) & & 4 (10) & 3 (9) & \\
Squamous cell carcinoma & 2 (4) & 0 (0) & & 3 (8) & 2 (6) & \\
Small cell carcinoma & 1 (2) & 1 (4) & & 0 (0) & 0 (0) & \\
Other & 5 (11) & 2 (8) & & 4 (10) & 0 (0) & \\
\text{Age, y} & & & & \\
Median (IQR) & 76 (64–79) & 66 (61–78) & 0.24 & 68 (57–75) & 72 (67–79) & 0.06 \\
Missing & 3 & 1 & & & & \\
\text{Passive smoke} & & & & \\
No exposure & 21 (47) & 17 (74) & 0.04 & 10 (32) & 4 (15) & 0.22 \\
Any exposure & 24 (53) & 6 (26) & & 21 (68) & 22 (85) & \\
Missing & 1 & 1 & & 8 & 8 & \\
\text{Passive smoke, pack-years} & & & & \\
No exposure & 21 (47) & 17 (74) & 0.08 & nd & nd & \\
<21 & 10 (22) & 3 (13) & & 20 (65) & 18 (69) & \\
21–52 & 11 (24) & 1 (4) & & 8 & 8 & \\
>52 & 3 (7) & 2 (9) & & & & \\
Missing & 1 & 1 & & & & \\
\text{Passive smoke (adult exposure)} & & & & \\
No exposure & nd & nd & & 11 (35) & 8 (31) & 0.78 \\
Any exposure & & & & 20 (65) & 18 (69) & \\
Missing & & & 6 & 6 & & \\
\text{Passive smoke (child exposure)} & & & & \\
No exposure & nd & nd & & 22 (71) & 13 (50) & 0.17 \\
Any exposure & 9 (29) & 13 (50) & & 8 & 8 & \\
Missing & & & & & & \\
\text{Radon exposure, Bq/m\textsuperscript{3}} & & & & \\
4.8–33.3 & 13 (30) & 5 (23) & 0.01 & nd & nd & \\
35.2–55.5 & 5 (11) & 9 (41) & & & & \\
56.2–82.7 & 9 (20) & 6 (27) & & & & \\
>82.7 & 17 (39) & 2 (9) & & & & \\
Missing & 2 & 2 & & & & \\
\text{Radon exposure, Bq/m\textsuperscript{3}} & & & & \\
Median (IQR) & 63.7 (30.5–94.1) & 46.5 (37.0–57.4) & 0.16 & nd & nd & \\
Missing & 2 & & & & & \\
\hline
\end{tabular}
\end{table}

Abbreviations: IQR, interquartile range; nd, not determined.

\textsuperscript{a}Five of the adenocarcinomas in the Mayo Clinic study were adenosquamous histology.

\textsuperscript{b}Fisher exact test.

\textsuperscript{c}Wilcoxon 2-sample test.
the Mayo Clinic never-smoker patient cohort. Previously, an inverse association with passive-smoke exposure as an adult or in childhood was observed (7). However, another study linked long-term exposure to passive smoking with excess EGFR mutations (8).

In conclusion, we observed a high frequency of EGFR mutations in lung tumors from never-smoking and long-term former-smoking women in the United States, but no association between EGFR mutations with passive-smoking or residential radon exposure.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: M. Taga, M.C.R. Alavanja, P. Yang, J. Jen, C.C. Harris
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Taga, N. Hagiwara, K.H. Vahakangas, W.P. Bennett, M.C.R. Alavanja, A. Lee, R. Diasio, E. Edell, A. Bungum, P. Yang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.E. Mechanic, M.A. Khan, P. Yang, C.C. Harris
Writing, review, and/or revision of the manuscript: M. Taga, L.E. Mechanic, N. Hagiwara, K.H. Vahakangas, W.P. Bennett, M.C.R. Alavanja, J.A. Welsh, E. Edell, P. Yang, J. Jen, C.C. Harris
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.E. Mechanic, J.A. Welsh, P. Yang
Study supervision: P. Yang, J. Jen, C.C. Harris
Biopspecimens acquisition: P. Yang
Design, development, and the analysis of the EGFR gene mutation status for all Mayo Clinic samples: J. Jen

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References
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