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Germline Mutations and Age at Onset of Lung Adenocarcinoma

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Abstract

Background: To identify additional at-risk groups for lung cancer screening, which targets persons with long history of smoking and thereby misses younger or non-smoking cases, we evaluated germline pathogenic variants (PVs) in lung adenocarcinoma patients for association with accelerated onset.

Methods: We assembled a retrospective cohort (1999–2018) of oncogenetic clinic patients with lung adenocarcinoma. Eligibility required family history of cancer, data on smoking, and germline biospecimen to screen via multi-gene panel. Germline PVs (*TP53/EGFR*; *BRCA2*; other Fanconi anemia (FA) pathway genes; non-FA DNA repair genes) were interrogated for association with age at diagnosis using an accelerated failure-time model.

Results: Subjects (n=187, age 28–89 years, female 72.7%, Hispanic 11.8%) included “smokers” (minimum 5 pack-years, n=65) and “non-smokers” (lighter ever-smokers n=18, never-smokers n=104). Overall, 26.7% of subjects carried 1–2 germline PVs: *TP53* (n=5), *EGFR* (n=2), *BRCA2* (n=6), other FA gene (n=11), other DNA repair gene (n=28). Adjusted for smoking, sex, and ethnicity, lung adenocarcinoma diagnosis was accelerated 12.2 (95% confidence limits 2.5, 20.6) years by *BRCA2* PVs, 9.0 (0.5, 16.5) years by *TP53/EGFR* PVs, and 6.1 (−1.0, 12.6) years by PVs in other FA genes. PVs in other DNA repair genes showed no association. Germline associations did not vary by smoking.

Conclusions: Among lung adenocarcinoma cases, germline PVs (*TP53, EGFR, BRCA2,* possibly other FA genes) may be associated with earlier onset. With further study, criteria for lung cancer screening may need to include carriers of high-risk PVs, and findings could influence precision therapy and reduce lung cancer mortality by earlier stage diagnosis.

Precis:

Among lung adenocarcinoma cases, we found germline pathogenic variants (TP53, EGFR, BRCA2, other FA genes) in 26.7% of our cohort. These pathogenic variants were associated with earlier onset of lung cancer with or without tobacco exposure.

Keywords

Adenocarcinoma; BRCA2; EGFR; TP53; Germline pathogenic variants; hereditary lung cancer

Introduction

Lung cancer is the leading cause of cancer mortality in men and women, accounting for more deaths than breast, colon, and prostate cancers combined.[1] Because early-stage lung cancer rarely causes symptoms, most lung cancers are not diagnosed until the disease is advanced. As a result, the 5-year survival remains below 20%.[2]

Most lung cancers are attributable to carcinogens in tobacco smoke. However, according to a recent study in the United States,[3] an increasing proportion (up to 15%) of non-small cell lung cancers (NSCLC) is diagnosed in patients who have never smoked. Yet current guidelines do not suggest lung cancer screening for never-smokers, greatly reducing their opportunity for early detection.

Individuals with an affected relative have been shown to have a higher risk of lung cancer.[4] Screening for inherited predisposition may prove useful for identifying individuals who are at elevated risk of lung cancer[5] and thus may be appropriate candidates for lung cancer screening. Recent studies showed that a minority of patients with lung adenocarcinoma carry germline PVs in cancer-associated genes, especially those in the Fanconi Anemia (FA) or DNA-repair pathways.[6] For example, *EGFR,* harbors the most common somatic mutation observed in NSCLC,[7] and a rare variant of *EGFR*, p.T790M,[8,9] is associated with a hereditary lung cancer syndrome that affects predominantly female never-smokers.[10] *TP53* is one of a dozen genome-maintenance genes whose transcript levels in normal bronchial epithelial cells are the basis for a biomarker-based risk score for lung cancer.[5] Inherited in germline, PVs in *TP53* cause a severe autosomal dominant susceptibility to multiple primary cancers (Li Fraumeni syndrome); after the core cancers (sarcoma, brain tumors, breast cancer, and adrenal cortical cancer), lung cancer is among the most frequent observed in *TP53* carriers.[11–13] PVs in genes within the FA and DNA-repair pathways are suspected of contributing to lung cancer but remain to be definitively linked to the disease. A known polymorphic nonsense variant in *BRCA2* (rs11571833; p.K3326*) has been associated with increased risk for lung cancer, especially squamous cell NSCLC, in genome wide association study (GWAS) data analyses[14,15] despite being non-pathogenic for breast or ovarian cancer.[16] To date, highly-penetrant *BRCA2* PVs that are associated with breast or ovarian cancer have not been associated with excess risk of lung cancer in family studies.[17,18]

Typically, germline PVs that increase the risk of cancer also cause earlier age at diagnosis (acceleration) of disease.[19] Accordingly, the current study evaluated the hypothesis that the disease occurs significantly earlier in carriers versus non-carriers of germline PVs in genes that are either commonly mutated in lung tumors (*EGFR, TP53*) or belong to pathways involved in DNA repair. Because effects of PVs may be specific to histologic subtypes of lung cancer, the current study focused exclusively on the most common histologic subtype, adenocarcinoma. The statistical analysis considered potential confounding factors and the possibility that associations with germline PVs might vary by history of smoking.

Materials and Methods

Eligibility and Recruitment

We assembled a retrospective cohort of patients with primary lung adenocarcinoma from an ongoing, IRB-approved registry of patients from oncogenetic clinics in the United States (ClinicalTrials.gov Identifier: NCT04185935; Clinical Cancer Genomics Community Research Network, CCGCRN[20,21]). The registry-derived cohort was supplemented with lung cancer patients from the City of Hope medical oncology clinic. Regardless of recruitment site, eligibility for the current study required a personal diagnosis of primary lung adenocarcinoma and a family history of cancer, defined as having a first- or second-degree relative ever diagnosed with cancer (other than non-melanoma skin cancer or intraepithelial carcinoma of the uterine cervix). Such family history was documented in a multi-generational pedigree. Further eligibility criteria included enrollment in the registry during 1999–2018, confirmation of lung adenocarcinoma by pathology report, known age at diagnosis, data on history of smoking, and availability of blood sample for comprehensive multi-gene panel testing. Selection into the cohort is summarized in the Supplemental Figure.

Genomic Sequencing

Genomic DNA was extracted from the blood samples and sequenced for coding variants using a custom-designed Agilent SureSelect targeted gene capture with 789 genes, that included EGFR and all those known to be associated with cancer (commonly on clinical panels), Fanconi anemia, as well as candidate genes involved in DNA repair and damage response, cell cycle regulation, apoptosis, and the mTOR, JAK–STAT, and RAS–MAPK pathways, as well as frequently mutated tumor suppressor and oncogenes from the Catalog of Somatic Mutations in Cancer (COSMIC) database,[20,21] The bait design included full exon, 5’ and 3’ untranslated regions, and splicing region coverage. Reaction products were evaluated using paired-end sequencing at an average of 100x coverage depth, as previously described.[20,21] Variants with an allele fraction ≥ 35% and read depth 5 were annotated using Ingenuity Variant Analysis using American College of Medical Genetics and Genomics Guidelines.[22] Pathogenic and likely pathogenic variants were analyzed together as pathogenic variants (PVs).

Statistical Analysis

Subjects with a history of smoking at least 5 pack-years were termed “smokers”, whether current or former. Included in that group were ever-smokers whose pack-year data were unavailable, because they had similar age at onset of lung cancer. The remaining subjects, termed “non-smokers”, included never-smokers as well as ever-smokers with fewer than 5 pack-years, because they had similar age of onset tothe never-smokers.

An accelerated failure-time model of age at diagnosis, specifying a Weibull distribution, was used to explore primary associations with 4 categories of germline PVs. Three categories of PVs were mutually exclusive: those in genes commonly mutated in lung cancer (*TP53, EGFR*); in *BRCA2*; and in FA pathway genes[23] other than *BRCA2* (of which current subjects carried PVs in *BLM, BRCA1, BRIP1, FAN1, MLH1, PMS2*). The fourth category

of PVs, those in DNA repair genes[24] (of which current subjects carried PVs in *APTX, ATM, CHEK2, ERCC2, FH, MRE11A, MSH2, MUTYH, OGG1, PARP4, PRKDC, RAD50, RAD54B, RAD54L, RECQL, RECQL4, RRM2B, WRN, XPA*) that are not included in the 3 preceding categories. The DNA repair category was not mutually exclusive with the preceding categories, because some subjects carried PVs in one of the latter DNA repair genes as well as in one of the 3 other categories. Because some subjects carried PVs in more than one DNA repair gene, this variable was coded as the number (0,1,2) of mutated genes in this category.

Potential covariates in the model were status as smoker versus non-smoker, sex, smoker-by-sex interaction, gene-by-smoker interaction, race (Asian vs non-Asian), and ethnicity (Hispanic vs non-Hispanic). Any covariate that did not improve the model's fit to the observed data, according to Aikake's Information Criteria, was omitted from the final analysis. Because of the exploratory nature of the analysis, statistical significance was not adjusted for multiple hypothesis testing.

Results

The demographic characteristics of subjects (n=187) were age 28–89 years, female 72.7%, Asian 26.7%, and Hispanic 11.8% (Table 1). Present in numbers too small to analyze separately were subjects who identified as African American (n=5), Native American (n=1), or Pacific Islander (n=3). Subjects included smokers (5-<20 pack-years, n=22; 20–50 pack-years, n=21; unrecorded pack-years, n=22) and non-smokers (never-smoker, n=104; light ever-smoker, <5 pack-years, n=18).

Overall, 26.7% (binomial 95% confidence interval: 20.4%−33.1%) carried at least 1 of the germline PVs under study. The number of PV carriers (listed by category in Table 2) is exceeded by the number of germline PVs (listed in the Supplemental Table), because 6 subjects carried more than one of these PVs. Specifically, one subject with *BRCA2* PV also carried a PV in DNA repair gene *ERCC2;* one subject with PV in another FA gene (*BRIP1*) also carried a PV in DNA repair gene *POLG;* and 4 subjects whose PVs were exclusively in other DNA repair genes each carried PVs in 2 such genes (either *ATM* and *MUTYH, ATM* and *RAD50, MUTYH* and *RAD54B,* or *MSH2* and *RAD54L*).

A plot of years lived until diagnosis of lung adenocarcinoma, by PV category, is shown in Figure 1. This plot is unadjusted for potential confounding factors, which are considered in the following multivariable model.

The model was adjusted for ethnicity, smoking history, sex, and their interaction. As shown in Table 2, the age at diagnosis of lung adenocarcinoma was accelerated by PVs in *BRCA2, TP53/EGFR,* and FA genes other than *BRCA2* but was unaffected by PVs in other DNA-repair genes. The associations with germline PVs did not vary by smoking history or by sex (as indicated by non-significant interaction terms, not shown). The model's fit to the observed data was not improved by separating light ever-smokers from never-smokers. Asian ancestry was unassociated with age at diagnosis and thus was omitted from the final model.

Discussion

Using comprehensive multi-gene panel screening of patients with lung adenocarcinoma, the current study explores the contribution of germline PVs in genes having an established or proposed association with lung cancer. As we report, heritable mutations in these genes appear to be fairly common among lung adenocarcinoma patients who have a family history of cancer. When present, certain of these PVs can accelerate the onset of lung adenocarcinoma, according to our exploratory model.

In that model, the gene whose pathogenic mutation shows the strongest association with age at onset is *BRCA2.* This novel finding suggests that carriers of PVs in *BRCA2* need to be monitored from early adulthood not only for breast and ovarian cancer but possibly also for lung cancer. As additional support for a *BRCA2* association with lung cancer, we cite our previous identification of *BRCA2* as the most common germline finding among lung cancer patients undergoing commercial genomic analyses of cell-free DNA.[25]

Another current association, linking PVs in *TP53* and *EGFR* with accelerated onset of lung adenocarcinoma, is consistent with the established roles of somatic mutations in these genes in the pathophysiology of lung cancer. Of note, the *EGFR* PVs detected in our subjects (p.Thr790Met and p.Arg776His) have been rarely reported to date.[8,9,19] In particular, to our knowledge, the germline PV p.Arg776His has been reported only once before.[26]

Of similar magnitude to the current associations with PVs in *BRCA2* and *TP53/EGFR,* but of lesser statistical significance, is the current association with PVs in other genes within the Fanconi anemia pathway.

Incidental findings from the current model include the observation that, regardless of smoking history, the onset of lung adenocarcinoma is accelerated among Hispanic individuals. However, there were relatively few Hispanic subjects in our cohort, and with one exception, all were female. Hence, further study will be required to confirm this observation, to verify that it extends to males also, and to identify environmental, occupational, lifestyle, genetic or epigenetic factors that may explain the association.

Additional incidental observations from the current model are that non-smokers have earlier onset of lung cancer than smokers, but only among males, and that females have earlier onset of lung cancer than males, but only among smokers. These observations, while they might be surprising, are consistent with the intensifying effect of women’s narrower airways on the established risk of lung cancer from tobacco smoking. Though smoking is a well-established risk factor for lung cancer, it does not necessarily follow that smokers develop lung cancer earlier than non-smokers do; in fact, our data indicate that the opposite is true.

This exploratory study has several limitations. The study is hypothesis generating and warrants validation from a separate cohort study. Restricted by design to cases of lung adenocarcinoma, the current study cohort cannot be used to estimate the relative risk of this disease among carriers of germline PVs. Instead, we have explored the extent to which germline PVs accelerate onset of this disease, a surrogate for predisposition.

The sample size, determined by the contents of the source registry, is not powered to include substantial numbers of PV carriers for each gene of interest, a goal that would have required studying thousands of subjects. Nor is the study powered to support the adjustment of statistical significance necessary to control the risk of error inherent in testing multiple hypotheses (here, the 4 groups of germline PVs). The small numbers of PVs among our subjects result in wide confidence intervals around the acceleration estimates we report and limit our ability to investigate whether PV-associated acceleration of lung cancer varies by history of smoking. Our multi-gene panel, although it included hundreds of cancer-associated genes, did not include all of the genes within the FA and DNA repair pathways; as a result, some subjects may have been misclassified as non-carriers of PVs in such genes. Finally, tobacco exposure was incompletely ascertained for many subjects: the number of pack-years could not be calculated for one third of the subjects classified as smokers, and data on non-smokers' exposure to environmental tobacco smoke (i.e., within the home) were not collected. As a result, a few subjects may have been misclassified on their status as *smokers* or *non-smokers* because of missing years of smoking data.

In conclusion, current findings propose a set of germline PVs, including *BRCA2,* for further investigation as heritable risk factors for lung adenocarcinoma. The disease acceleration we report for several PVs, when confirmed by additional studies, may warrant the modification of two sets of clinical guidelines. Specifically, eligibility criteria for lung cancer screening may need to include genetically predisposed individuals regardless of smoking history, and germline screening may be warranted for patients with lung cancer to screen for *BRCA2* and potentially other genes within the FA pathway. Ultimately, identification of an *EGFR* or *BRCA2* PV could influence precision therapy of lung cancer, and identification of at-risk persons through germline PVs could reduce lung cancer mortality by diagnosing the disease at an earlier, more curative stage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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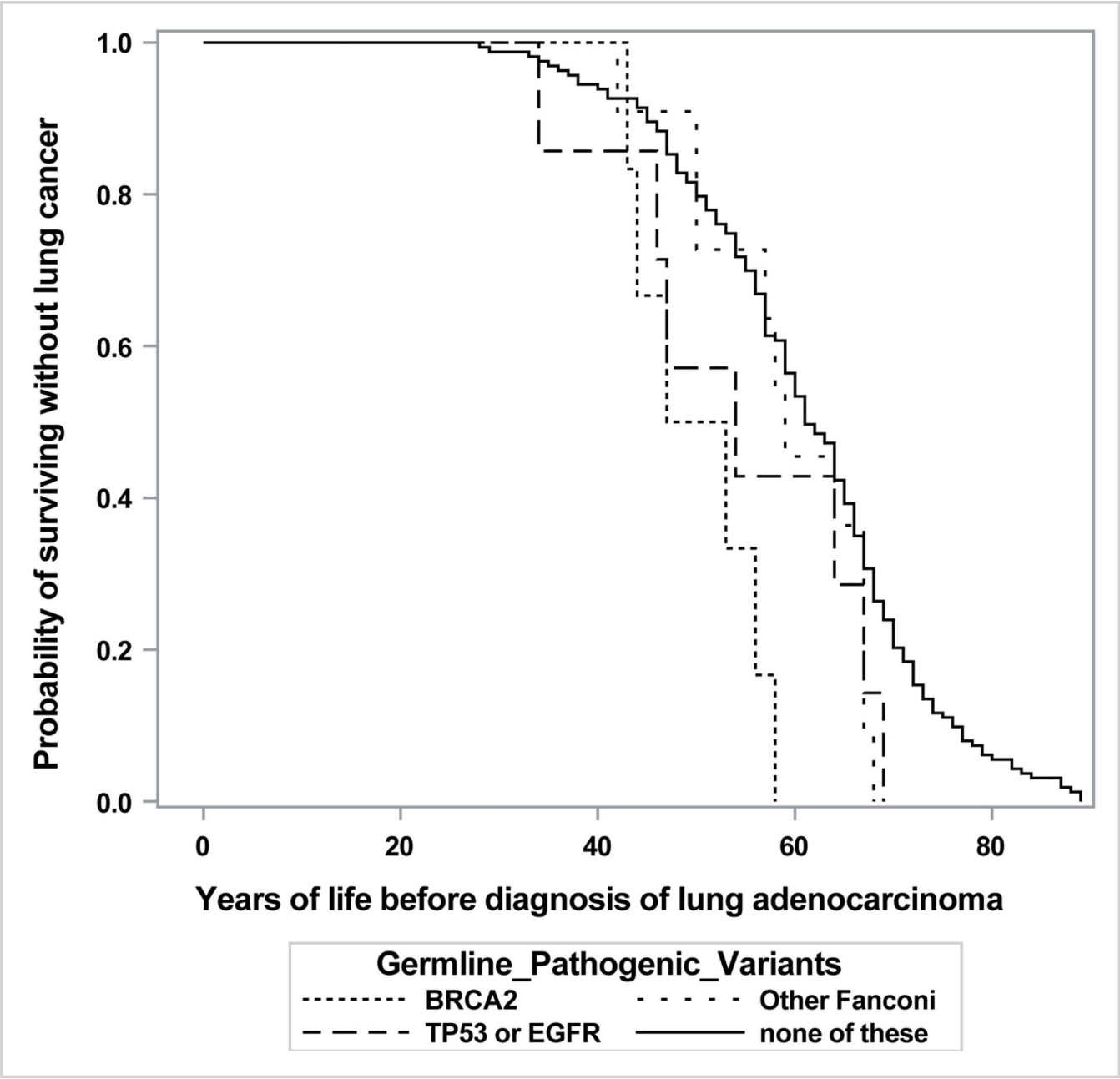

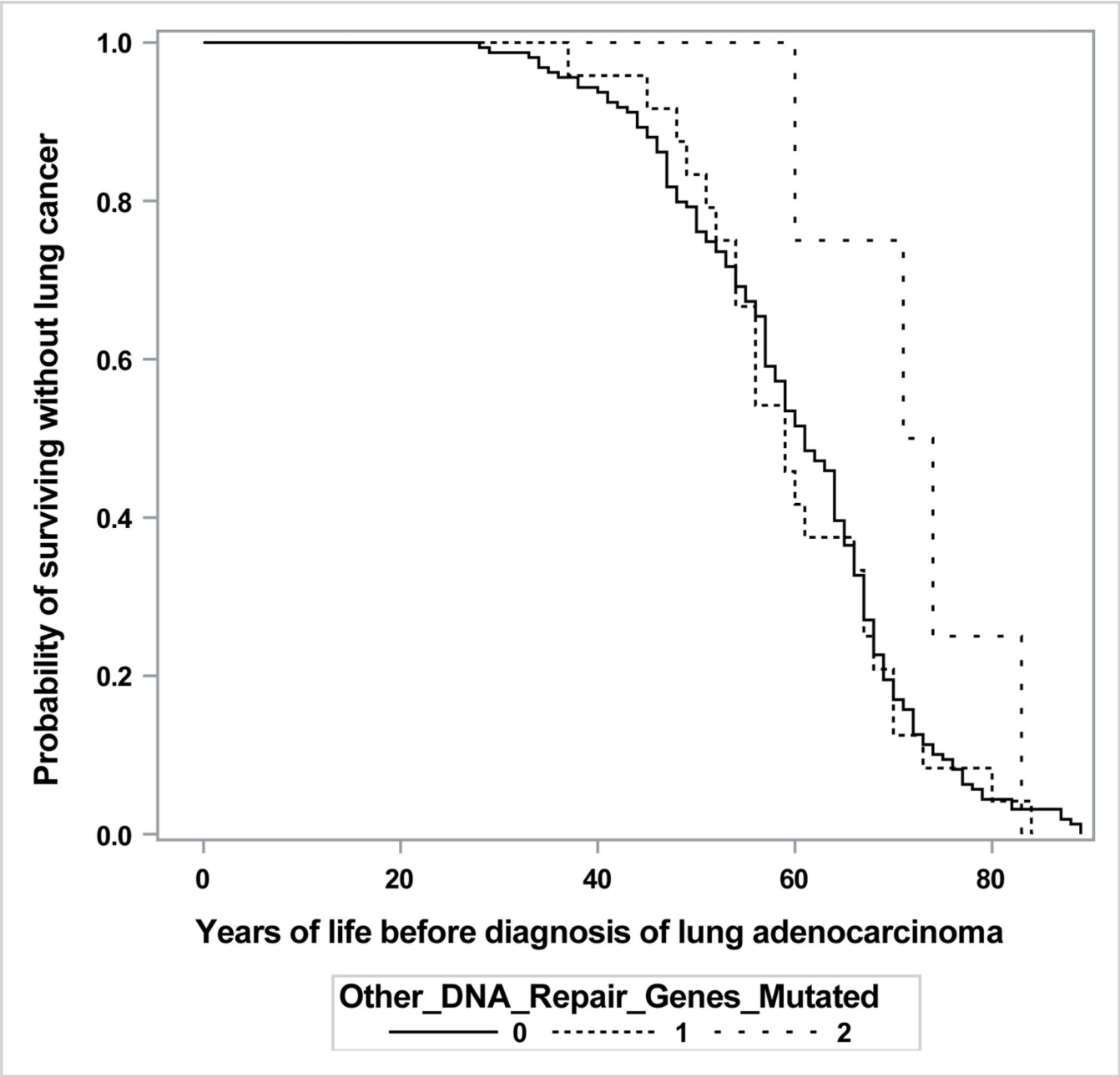

Figure 1.
Lung Adenocarcinoma Cohort (N=187): Years of Life until Diagnosis, by Germline Pathogenic Variant Status

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Table 1.

Subjects with Lung Adenocarcinoma

Characteristic	All Patients N=187 (Column %)	Patients with PVs N=50 (Column %)
History of Smoking		
Smoker		
Ever smoked at least 5 Pack-years	65 (34.8)	24 (48.0)
Nonsmoker		
Never smoked	104 (55.6)	22 (44.0)
Ever smoked less than 5 Pack-years	18 (9.6)	4 (8.0)
Sex		
Female	136 (72.7)	35 (70.0)
Male	51 (27.3)	15 (30.0)
Primary Ancestry (Self-identified)		
European	128 (68.4)	38 (76.0)
Asian	50 (26.7)	10 (20.0)
African	5 (2.7)	1 (2.0)
Pacific Islander	3 (1.6)	1 (2.0)
Native American	1 (0.5)	0
Ethnicity (Self-identified)		
Hispanic	22 (11.8)	7 (14.0)
Non-Hispanic	165 (87.2)	43 (86.0)

Table 2.

Lung Adenocarcinoma Cohort (N=187): Multivariable Model-estimated Age at Diagnosis and Acceleration in Onset

	N Subjects	Age at Diagnosis (95% Confidence Interval, CI)	p*	Acceleration in Age at Diagnosis (95% CI), Relative to Referent Group
Referent Group: Non-Hispanic Male Smoker Without Germline Pathogenic Variant Below	9	73.9 (68.5, 79.8)	-----	-----
Pathogenic Variants (Mutually Exclusive)				
In *BRCA2*	6	61.7 (53.3, 71.4)	0.015	−12.2 (−2.5, −20.6)
In *TP53* or *EGFR*	7	64.9 (57.4, 73.4)	0.039	−9.0 (−0.5, −16.5)
In FA Gene other than *BRCA2*	11	67.8 (61.4, 74.9)	0.090	−6.1 (+1.0, −12.6)
None of the above	163	referent		
Pathogenic Variants in Other DNA Repair Genes				
No	159	referent		
Yes, 1 Mutated Gene	24	72.2 (67.2, 77.6)	0.525	−1.7 (+3.7, −6.7)
Yes, 2 Mutated Genes	4	85.7 (72.7, 101.0)	0.078	+11.8 (+27.1, −1.2)
5+ Pack-Year Smoker, by Sex				
Smoker, Male	19	referent		
Non-Smoker, Male	32	61.4 (55.8, 67.5)	-----	−12.6 (−6.5, −18.1)
Smoker, Female	46	67.0 (61.3, 73.2)	-----	−7.0 (−0.8, −12.6)
Non-Smoker, Female	90	66.9 (59.9, 74.8)	-----	−7.0 (+0.9, −14.1)
Ethnicity				
Hispanic	22	65.8 (60.8–71.2)	-----	−8.1 (−2.7, −13.1)
Non-Hispanic	165	referent		

*P values are calculated for hypothesized risk factors but not for covariates.