Joint Effects of Germ-Line p53 Mutation and Sex on Cancer Risk in Li-Fraumeni Syndrome

Chih-Chieh Wu, Sanjay Shete, Christopher I. Amos, and Louise C. Strong

Abstract

Germ-line p53 mutations have been identified in most families with Li-Fraumeni syndrome (LFS). For germ-line p53 mutation carriers, there is considerable variability with respect to age of cancer onset and tumor type, suggesting that additional genetic effects influence the clinical severity and tumor spectrum. To identify factors that might contribute to the observed heterogeneity in time to onset, we used segregation analysis to analyze the joint effects of germ-line p53 mutations and risk modifier(s) on cancer incidence. We studied 159 kindreds, ascertained through probands who had been diagnosed with childhood soft-tissue sarcoma before 16 years of age, survived >3 years after diagnosis, and treated at The University of Texas M.D. Anderson Cancer Center (Houston, TX) from 1944 to 1975. This unique cohort has been followed systematically for >20 years and has had germ-line p53 mutation testing in probands and extended family members. The analyses revealed that germ-line p53 mutations and sex had significant effects on cancer risk: men with p53 mutations had 151-fold higher odds of developing cancer than did those without mutations [95% confidence interval (95% CI), 60-380], and women with p53 mutations had 1,075-fold higher odds than did those without mutations (95% CI, 358-3,229) and 7.1-fold higher odds of having cancer than did men with mutations (95% CI, 2.5-20.3). These findings provide quantitative cancer risk assessments for LFS families. (Cancer Res 2006; 66(16): 8287-92)

Introduction

Li-Fraumeni syndrome (LFS) is a rare familial cancer syndrome characterized by a high frequency of early-onset and diverse tumor types and an increased frequency of multiple primary tumors (1, 2). The initial description of the syndrome included the aggregation in families of soft-tissue sarcomas (STS), osteosarcomas, female breast cancer, brain tumors, leukemias, and adrenocortical carcinomas (3–7). Further studies have also shown greatly increased risks for many other common cancers, including prostate (7) and lung cancer (8). In addition, individuals from families with LFS have an increased propensity to develop multiple primary tumors (3).

Mutations in p53 are the most common tumor-specific genetic alteration in human neoplasms; they have been identified in >50% of human cancers, including many different cancer types. Germ-line mutations of p53 in chromosome 17p13.1 have been identified in 50% to 70% of families with LFS (9–11). As some LFS patients and their relatives affected with invasive cancers do not have germ-line mutations in p53, it is unlikely that mutations at a single locus, p53, can account for all clinical phenotypes of LFS. Even in the presence of a stable germ-line p53 mutation segregating in a family, the age of cancer onset and multiplicity of tumors within a family is variable, suggesting the presence of additional risk modifier(s). A small minority of LFS families with no p53 mutations has been noted to have mutations in CHEK2 (12). In addition, linkage to a region of chromosome 1q has been noted for some larger families with LFS who did not have CHEK2 or p53 mutations (13).

Given these observations, we proposed to determine the quantitative effects of p53 mutations on cancer risk and to evaluate the effects of modifier(s) of cancer risk.

Requests for reprints: Chih-Chieh Wu, Department of Epidemiology, Unit 1340, The University of Texas M.D. Anderson Cancer Center, 1155 Pressler Street, CPB4.3594, Houston, TX 77030. Phone: 713-745-3977; Fax: 713-792-8261; E-mail: ccwu@mdanderson.org.

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Materials and Methods

Study population. The study population used for this investigation consisted of 159 patients with LFS, who have been diagnosed before 16 years of age, survived ≥3 years after diagnosis, and treated at The University of Texas M. D. Anderson Cancer Center (Houston, TX) from 1944 to 1975, and their extended relatives, trimmed to include grandparents, aunts and uncles, parents, full siblings, and offspring of all probands. Kindreds in which a p53 germ-line mutation was identified were extended to include first-degree relatives of all individuals with p53 germ-line mutations. Because extension through mutation status was not done with respect to the phenotype, this approach to extending the family should not introduce an ascertainment bias during the segregation analysis.

For this analysis, we included all invasive cancers, except nonmelanoma skin cancers and in situ carcinoma. These disease criteria are broader than the classic LFS component tumors but are based on observations of diverse cancers occurring in excess in p53 germ-line mutation carriers (6–8). All cancers included in the analysis were confirmed by medical records or death certificates. Persons were considered at risk from date of birth to date of cancer diagnosis, death, lost to follow-up, study termination (December 31, 2001), or age of 75 years, whichever came first. The evaluation of cancer incidence was truncated at age of 75 years because of the limited reliability of cancer rates at older ages.

The final data set for the 159 kindreds consisted of 3,034 individuals, with 257 men and 215 women affected. This total is composed of 283 individuals from the 7 extended kindreds with a p53 germ-line mutation (7), including 63 mutation carriers (11 with no cancer), 1813 individuals from the remaining 100 kindreds for which the probands tested negative for p53, and 938 individuals from the 52 kindreds for which no sample was available for testing. Because germ-line p53 mutations are rare in general population and because the distributions of affected relatives in the 52 families are very close to those in 100 families that are p53 negative, we considered a total of 152 families as p53-negative families in our analyses. The number of males and females in each group was similar.

All probands (or “surrogates,” who were affected close relatives in cases in which the proband was deceased) were tested for p53. We then tested adult first-degree relatives of p53-positive probands. Next, the p53 mutation kindreds were extended to test at-risk adult relatives of p53 mutation carriers. In kindreds in which the proband tested negative for the p53 mutation, no other family members were specifically tested for p53 by full documentation, or age of 75 years, whichever came first. The evaluation of cancer diagnosis, death, lost to follow-up, study termination (December 31, 2001), or age of 75 years, whichever came first. The evaluation of cancer incidence was truncated at age of 75 years because of the limited reliability of cancer rates at older ages.

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Al phabets

The variables of regressive logistic models for genetic analysis used include qA, the frequency of the putative high-risk allele A; τu, the transmission probability of allele A for genotype u; z, the age adjustment coefficient; and b, the baseline variable for genotype u. The scale and location variables of the logistic distribution are z and β, respectively, where β is the natural logarithm of the odds of being affected versus being unaffected by genotype u when other components and covariates are zeros. Under the assumption of Mendelian inheritance, the values of β are fixed at τuAA = 1.0, τuAB = 0.5, and τuBB = 0.0. The effects of genotype AA are the same as those for genotype AB, as reflected by the baseline variables τuAA = τuAB for the Mendelian dominant model; βAB = βAB for the Mendelian recessive model; and βAB = 0.5 (βAA + βBB) for the Mendelian additive model. The effects of genotypes AA, AB, and BB decrease in that order, as reflected by βAA ≥ βAB ≥ βBB for the Mendelian decreasing (major-gene) model. The Mendelian arbitrary (major-gene) models do not put restrictions on the values of β. No-major-gene (sporadic) models assume that baseline risk is not influenced by genotype but can vary among populations.

The genetic and nongenetic covariates considered in the analysis were described as follows:

(a) Germ-line p53 mutation: those with mutations were coded as 1 and those with wild-type (WT) as 0. In 7 extended kindreds with a germ-line p53 mutation, 63 were carriers, 138 were WT, and 82 were at risk for being a mutation carrier but had unknown genotypes. Those with unknown genotypes in p53-positive families were given the values of probabilities of carrying p53 mutations. These were calculated using Bayes rule to incorporate the mutation statuses of any relatives who were tested for mutations within the families.

(b) Relationship cohort: the probands were coded as 0. Their first-, second-, and third-degree and higher degree relatives and marry-ins were coded as 1, 2, and 3, respectively.

(c) Generation cohort: the generation of probands was coded as 0. Their parents and grandchildren were coded as 1 and 2, respectively. Their parents were coded as −1, and their grandparents and earlier ancestors were coded as −2.

(d) Sex: males were coded as 0 and females as 1.

Hypothesis testing. The logarithm ln(L) of the maximum likelihood of the data was computed for each model. The likelihood ratio test (LRT) was used to test a specific model against the baseline model, which is usually the general model, in which the values of z are arbitrary to identify the best fit to the data for the general model. The specific model serves as the alternative model. The LRT was computed as follows: LRT = −2 ln(Lspecific) − ln(Lbaseline), where LRT approximately follows a χ² distribution with degrees of freedom equal to the difference in the numbers of independent variables estimated in the two models. Another method of model comparisons is Akaike’s information criteria (AIC), defined as AIC = −2 ln(L) + 2 (number of independent variable estimated). The model with the lowest AIC value and fewer estimated variables is generally considered the most parsimonious one. The LRT was also used to test for significance of the covariates included in the models where the model that included additional covariate(s) is regarded as the baseline model. Because some variables (such as some of the transmission variables) are fixed at boundaries for some hypothesis tests, the significance tests that we have applied yield conservative P values.

The genetic models for the modifier(s) of cancer risk underlying LFS remain unknown. Thus, it would not be appropriate to use highly restricted models for them, such as the Mendelian dominant, additive, or recessive models, when testing for the significance of covariates. We chose to test for the significance of covariates on the basis of the Mendelian decreasing model. The best fit of the Mendelian decreasing model suggests the presence of a single gene with reduced penetrance, which could be used to underlie multifactorial etiology (e.g., polygene or oligogene effects) accounting for many familial cancers (21). The decreasing model could also represent the composite effects of several genes or environmental factors that are strongly correlated among family members.
**Results**

We first assessed the significance of germ-line p53 mutations in our study. Letting the model that includes p53 mutations as the baseline model and the model with no covariates serves as the null model, the $\chi^2$ value for LRT with 1 degree of freedom was 122.09, giving $P < 0.0001$ and confirming the significance of p53 mutations on cancer risk. For the models including p53 as a covariate, the genetic model for the unobserved modifier of cancer risk is characterized by the coefficients of the logistic distribution variables $\alpha$ and $\beta$, which were defined previously. The results of the baseline model and null model for LRT testing are presented in columns 3 and 2 of Table 1, respectively.

Given the observations of Chompret al (22) and Hwang et al (7) about increased cancer risk in female p53 mutation carriers, we wanted to investigate the effects of sex on cancer risk in p53 germ-line mutation carriers. We used the covariate p53*sex, the product of p53 and sex, which estimates the excess of cancer risk in female carriers over male carriers (note that sex is coded as 1 for females and 0 for males in our scheme). Letting the sex-specific p53 effect model, which included p53 and p53*sex covariates, be the baseline model and the usual p53 effect model be the null model, as shown in columns 4 and 3 of Table 1, respectively, the $\chi^2$ value for LRT with 1 degree of freedom was 6.53, giving $P = 0.011$. The null hypothesis of the usual p53 effect model was rejected, suggesting that the sex difference on cancer risk is highly significant in people with germ-line p53 mutations differentially than the general population. This analysis shows that the sex-specific p53 effect model provides a better fit to the data.

Next, we incorporated the covariate of sex alone in the models with or without p53 mutations, but the results did not improve the fit of the model. To investigate the possible phenomenon of genetic anticipation or a birth cohort effect for mutation carriers, as suggested by some studies of LFS (23, 24), we included the covariates p53*generation (the product of p53 and generation effect) and generation in the analysis. According to the data shown in columns 6 and 7 of Table 1 and the comparisons with the sex-specific p53 model in column 4 using the LRT, p53*generation and generation were not significant factors in the models.

The use of the relationship cohort was based on our previous observation of familial cancer aggregations in first-degree relatives (3). Including the relationship covariate in the model did not significantly improve the likelihood value of the model as shown by comparing the two models in columns 4 and 8 of Table 1.

After we identified p53 and p53*sex to be the only two significant covariates in our segregation analysis, we further compared the sex-specific p53 model with its general model, for which the transmission probabilities $\tau$ are arbitrary (as opposed to the values of $\tau$ fixed at $\tau_{AA} = 1.0$, $\tau_{AB} = 0.5$, and $\tau_{BB} = 0.0$), as shown in column 5 of Table 1. Using the LRT, the $\chi^2$ value was 9.44 that gives $P = 0.024$ with 3 degrees of freedom, suggesting that the sex-specific p53 model was rejected by its general model at a 0.05 nominal significance level. Next, we compared the general sex-specific model with its environmental model, for which the values of $\tau$ are

### Table 1. Effects of covariates in segregation analysis

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<td>$\beta_{BB}$</td>
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<td>$\beta_{BA}$</td>
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<td>p53</td>
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<td>5.02</td>
<td>4.69</td>
<td>4.58</td>
<td>4.63</td>
<td>4.63</td>
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<tr>
<td>p53*sex</td>
<td>-</td>
<td>1.44</td>
<td>1.96</td>
<td>1.34</td>
<td>1.46</td>
<td>1.46</td>
<td>1.46</td>
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<tr>
<td>Generation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.20</td>
<td>-14</td>
<td>-14</td>
</tr>
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<td>Degrees of freedom</td>
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<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>-</td>
<td>122.09</td>
<td>6.53</td>
<td>9.44</td>
<td>1.06</td>
<td>0.08</td>
<td>0.91</td>
</tr>
<tr>
<td>$P$</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>0.011</td>
<td>0.024</td>
<td>0.303</td>
<td>0.777</td>
<td>0.340</td>
</tr>
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</table>

**NOTE:** $\tau_{AA} = 1.0$, $\tau_{AB} = 0.5$, and $\tau_{BB} = 0.0$ are fixed, except the general model on column 5.
The models presented in Table 1 were based on the assumption of sex dependence for genotype-specific baseline variable $\beta$. We analyzed the same data set, assuming sex independence for $\beta$, and found that each of the five models shown in the last five columns of Table 1 was better than the corresponding sex-independent model (data not shown). The associations between cancer incidence and the covariates, p53 or p53*sex, remained strong, and these were the only two significant covariates in the sex-independent models. These results could provide insight into the genetic basis of LFS and could be useful in designs of localizing non-p53 susceptibility genes or risk modifiers.

We also tested for genetic interaction between p53 mutations and unobserved modifier(s) of p53 for the 7 families with germ-line p53 mutations using SAGE 5.0 (27). Based on the Mendelian arbitrary model, the values of $(-2)^{9}$ likelihood were 796.25 for the general sex-specific p53 model with genotypic p53 mutation interaction and 802.87 for the corresponding model without genetic interaction. The $\chi^2$ value for LRT with 2 degrees of freedom was 6.62, which gives $P = 0.037$. This is modest evidence of an interaction between germ-line p53 mutations and p53 modifier for the seven families with p53 mutations. The variable coefficients of p53 and p53*sex, which are centered at mean 0.0, were 17.66 and 1.92, respectively. The variable coefficients of genotype-dependent effects of p53 were 0.08, 0.21, and 0.12, respectively. Accordingly, p53 and p53*sex had very strong effects, decreasing the ages of onset by 87 and 12 years, respectively. In contrast, the genotype-dependent effects of p53 in terms of age-of-onset changes were 0.41, 1.05, and 0.64 for p53A, p53AB, and p53B, respectively.

Although we found significant genetic interaction in the models at a 0.05 nominal significance level, the genotype-dependent fluctuations of p53 were very small compared with the main effects of p53 and p53*sex. The assessment of cancer risk attributable to significant covariates, which is assumed to be genotype independent, were essentially unchanged, whether or not we allowed for p53 interactions with a modifier locus. Therefore, the results we report in Table 1 are accurate. Furthermore, inclusion of the interaction effects led to flatness in the likelihood surface, which suggests that at least some of the variables in the segregation model became confounded with each other, so this extended model may not yield reliable results.

**Discussion**

We have a unique study population that was not ascertained because of characteristics suggestive of LFS (other than a proband with a childhood STS), and we have followed-up systematically the cohort for >20 years. Therefore, our analysis could well characterize and evaluate the cancer risk related to germ-line p53 mutations. Consequently, we applied a segregation analysis that allowed us to associate the simultaneous effects of germ-line p53 mutations and unobserved modifier(s) of cancer risk underlying LFS with cancer incidence in these families, possibly accounting for genetic modification of cancer risk among or within these families. This design jointly determines the most likely genetic model of modifier(s) of cancer risk contributing to LFS and the effects of p53 mutations and other genetic or nongenetic factors on cancer risk. Most clinical observations and case reports structured to identify germ-line p53 mutations determined the excess cancer risk in patients with mutations or their relatives using standardized incidence ratios. In contrast, we quantitatively evaluated the effects
of germ-line p53 mutations and other factors on cancer risk using Ols in a maximum likelihood segregation analysis, which was particularly designed for family data.

We identified a significantly higher cancer risk in people with germ-line p53 mutations in our models than in those without mutations. Individuals with germ-line p53 mutations had 151-fold higher odds of developing cancer than those with no mutations in men and 1,075-fold higher odds in women. More importantly, we found a significant sex difference in cancer risk among those with germ-line p53 mutations; women with mutations had 7.10-fold higher odds of having cancer than did men with mutations. These results indicate that those with mutations were younger at first cancer diagnosis than were those with no mutations and that age of onset at first cancer risk for women with mutations was significantly lower than in men as shown in Table 2.

In addition to the analysis done on the basis of the Mendelian decreasing model, as shown in Table 1, we also did this analysis using the Mendelian arbitrary models (the values of $\beta$ are arbitrary as opposed to the constraint $\beta_{AA} \geq \beta_{AB} \geq \beta_{BB}$ for the Mendelian decreasing model) and found similar results to the ones shown in Table 1. The only two significant covariates were p53 mutations and p53*sex. Based on the Mendelian arbitrary model, the values of $\beta$ are arbitrary as opposed to the constraint $\beta_{AA} \geq \beta_{AB} \geq \beta_{BB}$ for the Mendelian decreasing model (data not shown). These results suggest that additional modifier(s) of cancer risk, which was responsible for the familial cancer incidence, was more likely to be sex specific.

Some analytic approaches have suggested an anticipation or birth cohort effect in LFS (23, 24). Given that most of the offspring generations of our probands were <21 years, most had not undergone genetic testing, so we were limited in our ability to discriminate the effects of a p53 mutation carrier. Thus, our findings for the family relationship, generation, and p53*generation covariates should not be considered conclusive. Additional years of observation and genotyping are needed to confirm these findings and determine these effects.

We chose to model the age-specific risks depending on genotype and not the susceptibility variables based on consideration of biological processes causing an increased risk for cancer. According to either the two-stage or multistage models of cancer, genetic susceptibility for cancer predisposition affects the rate at which cancers develop not the baseline susceptibility. In addition, existing statistical treatments of other cancers using REGTL (21, 28) have typically shown that modeling genetic susceptibility as influencing the time to onset for cancer provides a better fit to data for familial cancers than modeling genetic susceptibility through baseline probabilities.

It is noteworthy that, given that all invasive cancers except nonmelanoma skin cancer and in situ carcinoma were included as a single combined phenotype in our analysis, we actually assumed that all cancer cases at 17 different sites were at equal risk in the setting of our models. The frequencies of site-specific incidence have been described in our previous work (7). The association between lung cancer and smoking-related cancer and cigarette

### Table 2. Age-specific cumulative cancer risk by p53 mutation, sex, and genotype

<table>
<thead>
<tr>
<th>Mutation/sex</th>
<th>Ages/genotype</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.898</td>
<td>0.399</td>
<td>0.060</td>
</tr>
<tr>
<td>&lt;40</td>
<td>0.988</td>
<td>0.861</td>
<td>0.371</td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.999</td>
<td>0.983</td>
<td>0.846</td>
</tr>
<tr>
<td>p53−</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;20</td>
<td>0.055</td>
<td>0.004</td>
<td>0.0004</td>
</tr>
<tr>
<td>&lt;40</td>
<td>0.351</td>
<td>0.039</td>
<td>0.004</td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.834</td>
<td>0.276</td>
<td>0.035</td>
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</table>
smoking in germ-line p53 mutation carriers was analyzed and published elsewhere (8). Other assessments of cancer risk for site-specific incidence seem impractical in our case because of the sample size limitations of site-specific data.

The identification of a sex difference in cancer risk in patients with germ-line p53 mutations is important. Although a difference in cancer risk by gender was first noted by Chompret et al. (22) and later by Hwang et al. (7), this approach provides a more quantitative assessment of the difference in risk. A future goal is to understand the mechanism by which sex modulates cancer risk among individuals with germ-line p53 mutations.

Hwang et al. (7) investigated cancer risk in germ-line p53 mutation carriers using the Kaplan-Meier methods, the Cox’s proportional hazards models, and the standardized incidence ratios. However, these methods only partially accommodate family structures in the analysis. The methods used by Hwang et al. adjust for intrafamilial correlations, assuming all individuals within a family have the same degree of correlation, and therefore do not allow for more complex correlation structure in the extended families we have studied, which included 56 relatives with mutations from 7 families. The maximum likelihood segregation models we used in this report are designed to analyze family data. In addition, the transmission of disease allele from one generation to another is efficiently modeled by our analysis.

Chompret et al. (22) used a different statistical approach to estimate the cancer risk in carriers of germ-line p53 mutations ascertained through childhood cancer patients. They included data from 268 index patients who were 18 years old or younger and had any type of solid malignant tumors; we ascertained families through probands with childhood STS. Furthermore, they did a mutation analysis mainly for the index patients and their parents, whereas we genotyped extended family members. In their study, 17 families had p53 mutations, and in our study, 7 of 107 families had p53 mutations. We studied 63 carriers of p53 mutations, so our estimated risks seem to be based on a larger number of carriers than those in Chompret et al’s study (22). They were the first to observe the increased cancer risk in women, which they attributed to breast cancer; data from Hwang et al (7) suggested that the excess risk could not be entirely attributed to female (breast and ovarian) cancers.

A full understanding of cancer prevention relies on more research to identify the genetic and nongenetic risk factors that contribute to cancer and to understand how these factors differentially influence cancer incidence in various population groups. Risk assessment for known cancer risk factors within various age groups would provide valuable inferences for clinical and genetic counseling. As an example, individuals who test positive for p53 mutations should undergo regular follow-up examinations and be monitored for potential symptoms leading to an early-stage diagnosis. Our study will provide more precise cancer risk estimates for patients with germ-line p53 mutations for genetic counseling and cancer prevention.

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References

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