[CANCER RESEARCH 52, 1695–1698, April 1, 1992]

p53 Mutations in Human Lung Tumors[1]

Carl W. Miller,[2] Kenneth Simon, Abdulkarim Aslo, Klaas Kok, Jun Yokota, Charles H. C. M. Buys, Masaaki Terada, and H. Phillip Koeffler

Department of Medicine, Division of Hematology/Oncology, UCLA School of Medicine, Los Angeles, California 90024 [C. W. M., K. S., A. A., K. K., H. P. K.]; Genetics Division, National Cancer Center Research Institute, Tsukii 5-chome, Chuo-ku, Tokyo, Japan [J. Y., M. T.]; and Department of Medical Genetics, University of Groningen, Antonious Deusinglaan 4, 9713 AW Groningen, The Netherlands [C. H. C. M. B.]

ABSTRACT

Mutation of one *p53* allele and loss of the normal *p53* allele [loss of heterozygosity (LOH)] occur in many tumors including lung cancers. These alterations apparently contribute to development of cancer by interfering with the tumor suppressor activity of *p53*. We directly sequenced amplified DNA in the mutational hot spots (exons 4–8) of *p53* in DNA samples from 40 lung cancers. Most (31 of 40) samples were preselected for LOH in the region of *p53*. We detected 23 *p53* mutations within these exons in 22 lung cancers; no *p53* mutations were found in normal tissue of the patients. One-half of the mutations were G to T transversions on the nontranscribed strand, consistent with mutagenesis by tobacco smoke. Mutations of C to A on the nontranscribed strand, which would result from G to T mutations on the transcribed strand, were detected only in one sample. Three of 23 mutations were nonsense mutations; to date, nonsense mutations of *p53* have not been reported in lung cancer. Mutation of this *p53*-coding region was detected in 20 of 27 small cell lung cancer samples, representing a 70% occurrence. Mutation of the *p53* gene is apparently very frequent in small cell lung cancers. When LOH in the *p53* region could be determined, complete concordance occurred between a sample having both a *p53* mutation and LOH in the region of *p53* (18 of 18 samples). Twelve samples of lung cancer had LOH in the region of *p53*, but the samples had no detectable *p53* mutations, suggesting either alterations outside the known mutational hot spots of *p53* or alterations of another unidentified tumor suppressor gene in the region of *p53*.

INTRODUCTION

p53 is a nuclear DNA-binding protein with properties of a transcriptional activator (1). *p53* was initially detected as a eukaryotic protein binding to simian virus 40 T-antigen and was later shown to interact with adenovirus E1b and papilloma virus E6. Evidence that *p53* is a tumor suppressor stems from *in vivo* and *in vitro* observations. Demonstrations of *p53* gene rearrangements in murine Friend erythroleukemia cells (2), human osteosarcomas (3), and various murine and human cell lines (4, 5) were early suggestions of inactivation of *p53* in tumors. LOH[3] of the short arm of chromosome 17, the site of the *p53* gene (6), was detected in many neoplasms, including those of lung, colon, brain, and bone, and suggested the presence of a tumor suppressor gene in this chromosomal region (7–11). At least 50% of lung cancers have LOH at 17p13 in the region of the *p53* gene (7, 8). Sequence analysis of the *p53* gene in a wide range of tumors, including lung carcinomas, demonstrated frequent mutations affecting codons 130 through 300 (12–14). These mutations probably inactivate tumor suppressor function of *p53*. In addition, transfection of cells with mutant *p53* complementary DNA clones caused transformation of cells and transfection of a normal *p53* gene in cells having a mutated *p53*, suppressed cellular transformation, and inhibited cell proliferation (15, 16).

MATERIALS AND METHODS

Samples. Loss of heterozygosity affecting chromosome band 17p13 was determined by analyzing matched blood/lung tumor pairs using pYNZ22 as a probe on Southern blots (17). DNA was isolated as described previously (18) from 40 lung cancer samples which consisted of 28 small cell lung cancers, 7 adenocarcinomas, 5 squamous cell tumors, and 1 large cell carcinoma. Normal tissue was analyzed in parallel for all individuals.

Amplification and Sequencing of DNA. Nucleotide sequences of *p53* between codons 109 through 307 (exons 4–8) were determined by direct sequencing of double-stranded polymerase chain reaction products. Exons were amplified separately using oligonucleotides based on published intron sequences (19).

Oligonucleotide sequences and fragment sizes for each exon were as follows: exon 4, AAAACCTACCAGGGCAGCTAC and CTCAGGGCAACGACCGTG yielding a fragment 91 bases in length; exon5,TTCCTCTTCCTGCAGTAC and GCCCCAGCTGCTCACCATCG giving a fragment 214 bases in length; exon 6, CACTGATTGCTCTTAGGTCTGGC and AGTTGCAAACCAGACCTCAGGCG for a fragment 144 bases long; exon 7,CTCCTAGGTTGGCTCTGACTGT and CAAGTGGCTCCTGACCTGGA giving a fragment 140 bases in length; exon 8, CCTATCCTGAGTAGTGGTAATCTAC and GTCCTGCTTGCTTACCTCGCTTAGT yielding a fragment of 166 bases. Fragments were purified from agarose gels using the phenol/freeze-thaw technique and sequenced using end-labeled oligonucleotides with modified T7 polymerase (20). In all cases, both strands were sequenced. With this approach, we are able to detect mutations only in samples containing less than equal quantities of normal DNA. Preselecting for samples in which loss of heterozygosity affecting chromosome 17p had been determined improved our chances of detecting any mutation.

RESULTS

Twenty-three mutations were found affecting *p53* codons 113 through 302 (Table 1 , Fig. 1). Mutations which were found at codons 113, 138, 143, 151, 160, 198, 203, 238, and 262 have not been described previously in lung cancer. Three of the 23 alterations were nonsense mutations; two of these were in codon 198. One sample, T31, had two G to T transversions: one immediately within intron 4 and the other immediately within intron 7. Another sample had a 30-base pair insertion at codon 276 (T16); the remaining changes were missense point mutations (Fig. 1). Eleven of the 23 mutations were G to T transversions of the nontranscribed strand; only one C to A transversion was detected on this strand in sample 1661T. The other changes included additional transversions and transitions. Silent mutations were detected affecting codons 203 and 302. A separate study demonstrated a mutation affecting intron 7 of sample Lu143 (21). Our approach focuses on the coding regions

Received 8/7/91; accepted 1/23/92.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] Supported in part by U. S. Public Health Service Grants DK42792, CA26038–11, CA42710, CA32737, and IRT370, the Weisz Family Foundation, 4E Leukemia Fund in memory of Marilyn Levine, and the Realtors of Real Estate Industry Division, and, in part, by a Grant-in-Aid for 10-Year Strategy Cancer Control from the Ministry of Health and Welfare of Japan.

[2] To whom requests for reprints should be addressed, at UCLA Division of Hematology/Oncology, 11–240 Factor Building, 10833 Le Conte Avenue, Los Angeles, CA 90024–1678.

[3] The abbreviation used is: LOH, loss of heterozygosity.

Downloaded from cancerres.aacrjournals.org on October 26, 2021. © 1992 American Association for Cancer Research.

and would have missed most intron mutations.

Mutations of the *p53* gene were detected in 20 of 27 (70%) small cell lung carcinomas, 1 of 7 adenocarcinomas, 1 of 5 squamous cell carcinomas, and the only sample of large cell carcinoma. No mutations were detected in any of the DNA samples from normal lung tissue of these patients (data not shown).

For all informative samples, *p53* mutation was invariably accompanied by LOH of chromosome 17p in the region of the *p53* locus (18 of 18 samples) (Table 1). Of note, 12 samples with LOH in the region of *p53* had no detectable abnormalities of *p53*.

DISCUSSION

We examined 40 lung tumors for alterations of the *p53* gene by direct sequencing of amplified DNA. Mutations were detected in 22 samples, including samples from 70% of the small cell and 23% of non-small cell lung cancers. In a previous study in which a variety of techniques (RNase protection, complementary DNA sequencing, and chemical mismatch cleavage analysis) was used, *p53* mutations were detected in 23 of 51 non-small cell carcinomas (22). Results of the combined data from our study and the above-mentioned study (22) are as follows: 12 of 22 (55%) squamous cell lung cancers, 3 of 6 (50%) large cell lung cancers, and 7 of 27 (26%) adenocarcinomas of the lung had detectable *p53* mutations. In addition, in a recent study (23), *p53*-coding mutations were found in 11 of 15 (73%) small cell cancers, which is nearly the same as our data (20 of 27 samples, 70%).

Our results reinforce several observations from prior studies (13, 14, 22, 23, 24), and we made several novel observations. From our sequence analysis, we found that 3 of the 23 changes of *p53* in our lung cancer samples caused nonsense mutations. Two of the nonsense mutations occurred at codon 198. Nonsense mutations of the *p53* gene in lung cancer have not been described. A prior study in which immunohistochemistry was used suggested that lung cancers with *p53* mutations have high expression of *p53* (24). This type of screening may miss samples with nonsense mutation if the alteration occurs proximal to the epitope of *p53* recognized by the antibody or if the change results in an ephemeral protein. Esophageal cancer is also a tobacco-related neoplasia, and nonsense mutations are frequent in this cancer (25).

The predominant nucleotide change, accounting for 50% of the mutations, was G to T transversion. This frequency is very close to what was found in previous analyses of lung cancers (22, 23). Benzo(*a*)pyrene is one of the major mutagens in cigarette smoke, and it causes G to T transversions in DNA

Table 1 *p53 mutations in lung cancer*

Lung samples			Site of mutation		Mutational change	
Name	Diagnosis	Exon	Codon	Base	Amino acid	LOH[a] p17
211T	AD[b]	4	113	TTC to TGT	Phe to Cys	Yes
T51	SC	5	138	GCC to CCC	Ala to Pro	Yes
T67	SQ	5	143	GTG to TTG	Val to Leu	un
1661T	SC	5	151	CCC to CAC	Pro to His	Yes
1492M	SC	5	157	GTC to TTC	Val to Phe	Yes
T211	SC	5	160	ATG to ATT	Met to Ile	nd
1591T	SC	6	198	GAA to TAA	Glu to end	Yes
T36	SC	6	198	GAA to TAA	Glu to end	nd
T57	SC	6	203	GTG to GTT	Val to Val	Yes
1523M	SC	6	205	TAT to TGT	Tyr to Cys	Yes
T143	SC	6	220	TAT to TGT	Tyr to Cys	Yes
N521T1	LG	7	238	TGT to TGA	Cys to end	Yes
271T	SC	7	244	GGC to TGC	Gly to Cys	Yes
T35	SC	7	248	CGG to CTG	Arg to Leu	Yes
1622M	SC	8	272	GTG to CTG	Val to Leu	Yes
1531T	SC	8	273	CGT to CAT	Arg to His	Yes
T16	SC	8	276	Insert of 30 base pairs		nd
1651T	SC	8	277	TGT to GGT	Cys to Gly	Yes
1481T	SC	8	282	CGG to CCG	Arg to Pro	Yes
1582M	SC	8	286	GAA to GGA	Glu to Gly	Yes
T15	SC	8	302	GGG to GGT	Silent	Yes
T31	SC		Mutation in introns 4 and 7[c]			Yes
Lu143	SC		Intron 7 mutation previously described (21)			Yes
T28	AD					No
T65	AD					No
T83	AD					Yes
N531T	AD					Yes
N511TI	AD					Yes
N141TI	AD					Yes
1602M	SC					Yes
T47	SC					Yes
T188	SC					nd
1107T	SC					Yes
12441T	SC					Yes
1631T	SC					Yes
1641T	SC					Yes
T68	SQ					un
T77	SQ					Yes
T108	SQ					No
1671T	SQ					Yes

[a] LOH on short arm of human chromosome 17.

[b] AD, adenocarcinoma; SC, small cell carcinoma; SQ, squamous cell carcinoma; LG, large cell carcinoma; un, uninformative (homozygous in normal tissue); end, stop codon; nd, not done.

[c] Two G to T transversions were detected in sample T31: one at the intron 4-exon 5 junction (CAG.TAC to CAT.TAC) and the other at the intron 7-exon 8 junction (TAG.TGG to TAT.TGG).

Downloaded from cancerres.aacrjournals.org on October 26, 2021. © 1992 American Association for Cancer Research.

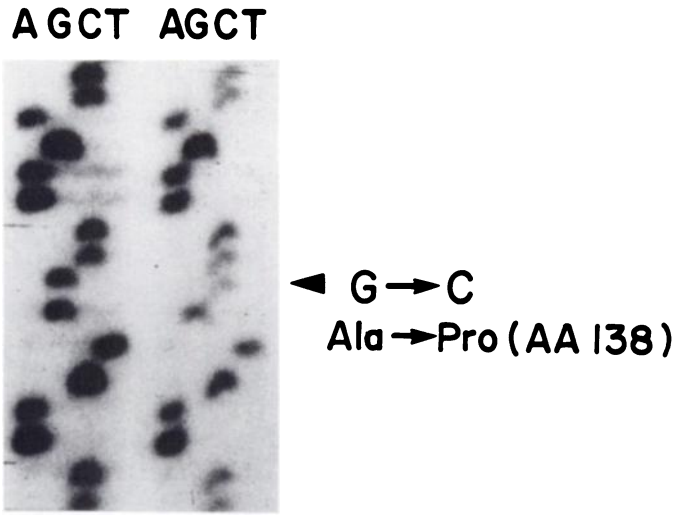

Fig. 1. Missense mutation at *p53* codon 138 in small cell lung cancer. Sequence of the nontranscribed strand of *p53* exon 5 is shown in a sample (T51) with normal sequence on the left and with a mutation on the right. This G to C transversion at codon 138 changes alanine (GCC) to proline (CCC).

(26). As previously noted, a strand bias occurs with the mutated guanine being on the nontranscribed strand (22). Transversions of C to A on the nontranscribed strand should be noted in lung tumors if mutations of G to T also occurred on the transcribed strand of DNA; only one such change was detected. Other studies of *p53* alterations in lung cancers did not detect C to A transversions on the nontranscribed strand (22–24). Mutagenesis experiments suggest that the nontranscribed strand is more frequently altered, perhaps because of preferential repair of the transcribed strand (27–29). In contrast, transition mutations of *p53* at guanine residues do not show a strand bias in either lung or breast cancers (30).

Several codons have been identified as hot spots for *p53* mutations in a variety of tumors (30). Mutation at codon 175 of *p53* is observed in about 25% of colorectal carcinomas and has been described in sarcomas, breast tumors, and leukemias (31–34). This codon is predominantly activated by G to A transitions, but G to T transversions have also been described (33). The mutational hot spot at codon 175 may be due to the innate rate of mutation of methylcytosine in normally methylated CG pairs. To our knowledge, no mutations of codon 175 of *p53* in lung cancers have been reported. The reason for this is unclear. It could be due to structural features of the DNA; for example, codon 175 may be demethylated in lung tissue. Alternatively, mutation at codon 175 might not contribute to oncogenesis in lung tissue.

All informative samples that had *p53* mutations also had LOH in the region of *p53* (18 of 18 samples, excluding samples in which LOH could not be evaluated). As expected, these samples did not contain a normal *p53* allele. The lack of a normal allele suggests that a growth advantage occurs with loss of the remaining normal *p53* allele. This is consistent with the paradigm that many cancers are associated with mutation of one allele of a tumor suppressor gene (*e.g.*, *p53*) and loss of the remaining allele. In a previous study, however, both the normal and mutant *p53* alleles were detected in 6 of 23 lung tumor samples (22). This could represent either contaminating normal tissue or mutant *p53* behaving as a dominant negative protein by perhaps binding and inactivating normal *p53*. *In vitro* and transgenic mice studies have shown that mutant *p53* can act in a dominant negative fashion (35, 36).

In addition, we found that 12 of 31 lung tumor samples having LOH affecting the region of *p53* had no alteration of *p53* in exons 4 through 8. Also, in a previous study of lung cancer, no detectable mutations of *p53* were noted in samples with LOH in the region of *p53* (22). Perhaps in these samples, an alteration occurs elsewhere in the *p53* gene. One possibility, as illustrated by sample Lu143 (mutation in intron 7) and sample T31 (mutations in introns 4 and 7), is that mutations may occur within the introns, perhaps affecting RNA metabolism (21, 37). Another possibility is that an unidentified tumor suppressor gene is in the region of *p53*, and it is often aberrant in lung tumors.

We sequenced genomic DNA from normal cells of our patients; no *p53* mutations were observed. This confirms prior results (22, 23) that most lung cancers have somatically acquired *p53* mutations.

REFERENCES

1. Levine, A. J., Momand, J., and Finlay, C. A. The p53 tumour suppressor gene. Nature (Lond.), *351:* 453–456, 1991.
2. Chow, V., Ben-David, Y., Bernstein, A., Benchimol, S., and Mowat, M. Multistage Friend erythroleukemia: independent origin of tumor clones with normal or rearranged p53 cellular oncogenes. J. Virol., *61:* 2777–2781, 1987.
3. Masuda, H., Miller, C., Koeffler, H. P., Battifora, H., and Cline M. J. Rearrangement of the p53 gene in human osteogenic sarcomas. Proc. Natl. Acad. Sci. USA, *84:* 7716–7719, 1987.
4. Wolf, D., Harris, N., and Rotter, V. Ableson murine leukemia virus transformed cells that lack p53 protein synthesis express aberrant p53 mRNA species. Mol. Cell. Biol., *4:* 552–558, 1985.
5. Wolf, D., and Rotter, V. Major deletions in the gene encoding the p53 tumor antigen cause lack of p53 expression in HL-60 cells. Proc. Natl. Acad. Sci. USA, *82:* 790–794, 1985.
6. Miller, C., Mohandas, T., Wolf, D., Prokocimer, M., Rotter, V., and Koeffler, H. P. The p53 gene is located on the short arm of chromosome 17 in humans. Nature (Lond.), *319:* 738–784, 1986.
7. Yokota, J., Wada, M., Shimosato, Y., Terada, M., and Sugimura, T. Loss of heterozygosity on chromosomes 3, 13, and 17 in small-cell carcinoma and on chromosome 3 in adenocarcinoma of the lung. Proc. Natl. Acad. Sci. USA, *84:* 9252–9256, 1987.
8. Weston, A., Willey, J. C., Modali, R., Sugimura, H., McDowell, E. M., Resau, J., Light, B., Haugen, A., Mann, D. L., and Trump, B. F. Differential DNA sequence deletions from chromosomes 3,11, 13, and 17 in squamous-cell carcinoma, large-cell carcinoma, and adenocarcinoma of the human lung. Proc. Natl. Acad. Sci. USA, *86:* 5099–5103, 1989.
9. Lothe, R. A., Nakamura, Y., Woodward, S., Gedde-Dahl, T. Jr., and White, R., VNTR (variable number of tandem repeats) markers show loss of chromosome 17p sequences in human colorectal carcinomas. Cytogenet. Cell Genet., *48:* 167–169, 1988.
10. James, C. D., Carlbom, E., Nordenskjold, M., Collins, V. P., and Cavenee, W. K. Mitotic recombination of chromosome 17 in astrocytomas. Proc. Natl. Acad. Sci. USA, *86:* 2858–2862, 1989.
11. Toguchida, J., Ishizaki, K., Nakamura, Y., Sasaki, M. S., Ikenaga, M., Kato, M., Sugimoto, M., Kotoura, Y., and Yamamuro, T. Assignment of common allele loss in osteosarcoma to the subregion 17p13. Cancer Res., *49:* 6247–6251, 1989.
12. Baker, S. J., Fearon, E. R., Nigro, J. M., Hamilton, S. R., Preisinger, A. C., Jessup, J. M., vanTuinen, P., Ledbetter, D. H., Barker, D. F., Nakamura, Y. *et al.* Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. Science (Washington DC), *244:* 217–221, 1989.
13. Takahashi, T., Nau, M. M., Chiba, I., Birrer, M. J., Rosenberg, R. K., Vinocour, M., Levitt, M., Pass, H., Gazdar, A. F., and Minna, J. D. p53: a frequent target for genetic abnormalities in lung cancer. Science (Washington DC), *246:* 491–494, 1989.
14. Nigro, J. M., Baker, S. J., Preisinger, A. C., Jessup, J. M., Hostetter, R., Cleary, K., Bigner, S. H., Davidson, N., Baylin, S., Devilee, P., Glover, T., Collins, F. S., Weston, A., Modasli, R., Harris, C. C., and Vogelstein, B. Mutations in the p53 Gene occur in diverse tumor types. Nature (Lond.), *342:* 705–708, 1989.
15. Finlay, C. A., Hinds, P. W., and Levine, A. J. The p53 proto-oncogene can act as a suppressor of transformation. Cell, *57:* 1083–1093, 1989.
16. Eliyahu, D., Michalovitz, D., Eliyahu, S., Pinhasi-Kimchi, O., and Oren, M. Wild-type p53 can inhibit oncogene-mediated focus formation. Proc. Natl. Acad. Sci. USA, *86:* 8763–8767, 1989.
17. Miller, C. W., Aslo, A., Tsay, C., Slamon, D., Ishizaki, K., Toguchida, J., Yamamuro, T., Lampkin, B., and Koeffler, H. P. Frequency and structure of p53 rearrangements in human osteosarcoma. Cancer Res., *50:* 7950–7954, 1990.
18. Nakamura, Y., Ballard, L., Leppert, M., O'Connell, P., Lathrop, G. M.,

Downloaded from cancerres.aacrjournals.org on October 26, 2021. © 1992 American Association for Cancer Research.

Lalouel, J. M., and White, R. Isolation and mapping of a polymorphic DNA sequence (pYNZ22) on chromosome 17p: D17S30. Nucleic Acids Res., *16:* 5707, 1988.

19. Buchman, V. L., Chumakov, P. M., Ninkina, N. N., Samarina, O. P., and Georgiev, G. P. A variation in the structure of the protein-coding region of the human p53 gene. Gene, *70:* 245–252, 1988.
20. Lubbert, M., Mirro, J., Jr., Miller, C. W., Kahan, J., Isaac, G., Kitchingman, G., Mertelsmann, R., Herrmann, F., McCormick, F., and Koeffler, H. P. N-*ras* gene point mutations in childhood acute lymphocytic leukemia correlate with a poor prognosis. Blood, *75:* 1163–1169, 1990.
21. Sameshima, Y., Akiyama, T., Mori, N., Mizoguchi, H., Toyoshima, K., Sugimura, T., Terada, M., and Yokota. J. Point mutation of the p53 gene resulting in splicing inhibition in small cell lung carcinoma. Biochem. Biophys. Res. Commun., *173:* 697–703, 1990.
22. Chiba, I., Takahashi, T., Nau, M. M., D'Amico, D., Curiel, D. T., Mitsudomi, T., Buchhagen, D. L., Carbone, D., Piantadosi, S., Koga, H., Reissman, P. T., Slamon, D. J., Holmes, E. C., and Minna, J. D. Mutations in the p53 gene are frequent in primary, resected non-small cell lung cancer. Lung Cancer Study Group. Oncogene, *5:* 1603–1610, 1990.
23. Takahashi, T., Takahashi, T., Suzuki, H., Hida, T., Sekido, Y., Ariyoshi, Y., and Ueda, R. The p53 gene is very frequently mutated in small-cell lung cancer with a distinct nucleotide substitution pattern. Oncogene, *6:* 1775–1778, 1991.
24. Iggo, R., Gatter, K., Bartek, J., Lane, D., and Harris, A. L. Increased expression of mutant forms of p53 oncogene in primary lung cancer. Lancet, *335:* 675–679, 1990.
25. Hollstein, M. C., Metcalf, R. A., Welsh, J. A., Montesano, R., and Harris, C. C. Frequent mutation of the p53 gene in human esophageal cancer. Proc. Natl. Acad. Sci. USA, *87:* 9958–9961, 1990.
26. Mazur, M., and Glickman, B. W. Sequence specificity of mutations induced by benzo:a:pyrene-7,8-diol-9,10-epoxide at endogenous *aprt* gene in CHO cells. Somat. Cell Mol. Genet., *14:* 393–400, 1988.
27. Hanawalt, P. C. Preferential DNA repair in expressed genes. Environ. Health Perspect., *76:* 9–14, 1987.
28. Bohr, V. A., Phillips, D. H., and Hanawalt, P. C. Heterogeneous DNA damage and repair in the mamalian genome. Cancer Res., *47:* 6426–6436, 1987.
29. Mellon, I., Spivak, G., and Hanwalt, P. C. Selective removal of transcription-blocking DNA damage from the transcribed strand of the mammalian DHFR gene. Cell, *51:* 241–249, 1987.
30. Hollstein, M., Sidransky, D., Vogelstein, B., and Harris, C. C. P53 mutations in cancers. Science (Washington DC), *253:* 49–53, 1991.
31. Baker, S. J., Preisinger, A. C., Jessup, J. M., Paraskeva, C., Markowitz, S., Willson, J. K., Hamilton, S., and Vogelstein, B. p53 gene mutations occur in combination with 17p allelic deletions as late events in colorectal tumorigenesis. Cancer Res., *50:* 7717–7722, 1990.
32. Mulligan, L. M., Matlashewski, G. J., Scrable, H. J., and Cavenee, W. K. Mechanisms of p53 loss in human sarcomas. Proc. Natl. Acad. Sci. USA, *87:* 5863–5867, 1990.
33. Prosser, J., Thompson, A. M., Cranston, G., and Evans, H. J. Evidence that p53 behaves as a tumour suppressor gene in sporadic breast tumours. Oncogene, *5:* 1573–1579, 1990.
34. Cheng, J., and Haas, M. Frequent mutations in the p53 tumor suppressor gene in human leukemia t-cell lines. Mol. Cell. Biol., *10:* 5502–5509, 1990.
35. Finlay, C. A., Hinds, P. W., Tan, T. H., Eliyahu, D., Oren, M., and Levine, A. J. Activating mutations for transformation by p53 produce a gene product that forms an hsc70-p53 complex with an altered half-life. Mol. Cell. Biol., *8:* 531–539, 1988.
36. Lavigueur, A., Maltby, V., Mock, D., Rossant, J., Pawson, T., and Bernstein, A. High incidence of lung, bone, and lymphoid tumors in transgenic mice overexpressing mutant alleles of the p53 oncogene. Mol. Cell. Biol., *9:* 3982–3991, 1989.
37. Takahashi, T., D'Amico, D., Chiba, I., Buchhagen, D. L., and Minna, J. D. Identification of intronic point mutations as an alternative mechanism for p53 inactivation in lung cancer. J. Clin. Invest., *86:* 363–369, 1990.

Downloaded from cancerres.aacrjournals.org on October 26, 2021. © 1992 American Association for Cancer Research.

AACR American Association for Cancer Research

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

p53 Mutations in Human Lung Tumors

Carl W. Miller, Kenneth Simon, Abdulkarim Aslo, et al.

Cancer Res 1992;52:1695-1698.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/52/7/1695

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/52/7/1695. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cancerres.aacrjournals.org on October 26, 2021. © 1992 American Association for Cancer Research.