Letters to the Editor

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p53 Variants Predisposing to Cancer Are Present in Healthy Centenarians

To the Editor:

Cancer results from the expansion of cell clones that progressively lose control of proliferation, differentiation, and death, owing to accumulation of mutational events in genes that control the cell cycle and apoptosis. Nuclear protein p53 is thought to play a major role in malignancy, since it induces genes that determine apoptosis and cell-cycle arrest, interacts with proteins employed in DNA repair, and binds to DNA strand breaks. As expected, somatic mutations in p53 are found in a variety of human cancers. Mutations are predominantly inactivating, thus eliminating the "guardian of the genome" from the proliferating cells. Germ-line mutations of p53 also have been described as the molecular basis of a rare familial cancer-prone syndrome, Li-Fraumeni syndrome. At the population level, common variants (polymorphisms) of p53 are present. In particular, a C→G transversion leads to a proline-to-arginine change at p53 codon 72. Several studies have reported data regarding the association of the codon 72 variants with susceptibility to a variety of human cancers, such as breast cancer, lung cancer, and colorectal neoplasia (Birgander et al. 1995; Sjalander et al. 1996). Some reports suggest that Arg/Pro72 alleles should be considered as markers in linkage disequilibrium with other sites able to modulate cancer risk (Sjalander et al. 1995). Recently, a new insight into the role of codon 72 in human cancers has been reported by Storey et al. (1998). In their analysis, the authors found that a majority (76%) of women affected by human papillomavirus (HPV)–induced cervical carcinoma were homozygous for Arg72 alleles, compared with a frequency of 37% among unaffected women. In addition, when functional analysis of p53 variants was performed, the authors found that a p53 protein carrying an arginine at codon 72 binds more effectively to HPV oncoprotein E6 and is degraded and inactivated more rapidly by the proteasome pathway. The result is an estimated sevenfold risk of developing cervical cancer, for people homozygous for Arg72, when infected by HPV that is able to produce E6 protein. Overall, the available data in the literature suggest that p53 variants may be considered as risk factors for some of the major neoplastic diseases in humans, such as lung, colorectal, breast, and cervical cancer, and are expected to affect survival. Hence, an underrepresentation of p53 variants involved in cancer risk would be expected in a group of people who reach very old age in good health and who have escaped any overt cancer disease. Accordingly, healthy centenarians of both sexes were studied, to test this prediction, and the results were compared with those obtained from the study of a group of younger people.

The centenarians and the controls in our study were basically those studied in a previous investigation, in which significant differences in the frequency of apolipoprotein B (ApoB) VNTR alleles were found between the two groups (De Benedictis et al. 1997). The sample of centenarians comprised 176 healthy unrelated subjects (53 males and 123 females) from northern and southern Italy, and the health status of each was assessed as described elsewhere (Capurso et al. 1997). The control group comprised 204 younger unrelated subjects (113 males and 91 females, 20–60 years of age) randomly collected from northern and southern Italy. The ancestry in the specific geographic area of the subjects included in this study was checked as far back as the grandparental generation. In table 1 the frequencies of p53 codon 72 alleles and genotypes in the younger controls and the centenarians are shown. No difference between the two groups was found. Moreover, no difference in allelic and genotypic distributions, between the centenarians and the younger controls, was found when sex and geographic origin were considered in the analysis or when the group of younger controls was split into two subgroups (<40 and ≥ 40 years of age) (data not shown).

Several explanations can account for the results reported here. First, the most direct explanation is that Arg/Pro72 alleles are neutral and do not exert any censoring, with regard to susceptibility to cancer and life expectancy. This hypothesis is compatible with the cautious conclusions of a recent meta-analysis, which points out that a consensus about the role of p53 variants in human cancer has yet to be reached (Weston and God-

Table 1

Allelic and Genotypic Frequencies of p53 Codon 72 Polymorphism

	No. (%) of Younger Controls [n = 204]	No. (%) of Centenarians [n = 176]
p53 Allele:[a]		
Pro72	128 (31.4)	101 (28.7)
Arg72	280 (68.6)	251 (71.3)
p53 Genotype:[b]		
Pro72/Pro72	18 (8.8)	12 (6.8)
Arg72/Pro72	92 (45.1)	77 (43.8)
Arg72/Arg72	94 (46.1)	87 (49.4)

NOTE.—Hardy-Weinberg equilibrium (HWE) of p53 genotypes was assessed by exact tests. Both groups were in HWE: younger controls, $P = .46$; and centenarians, $P = .61$. χ^2 tests for comparison of allelic and genotypic distributions were performed by use of Monte Carlo algorithms implemented by means of the Statistical Product and Service Solutions package.

[a] $\chi^2 = 0.64$, df 1, $P = .42$.

[b] $\chi^2 = 0.74$, df 2, $P = .68$.

bold 1997). Second, we can assume that p53 codon 72 Arg/Pro alleles are not neutral. In view of this hypothesis, our data on healthy centenarians suggest that the long-term consequences of p53 codon 72 Arg/Pro alleles on survival are negligible, even though they are related to increased cancer risk. However, additional data regarding the incidence of and mortality rate for p53-related cancers in the cohort studied and the relative risk of developing these diseases, for different p53 allelic variants, are needed in order to reject the above-mentioned hypothesis. On the other hand, recent data indicate that p53 polymorphisms appear to modulate an individual's risk of developing cancer only when peculiar conditions occur (i.e., a particular viral infection). In this case, only a small proportion of people who carry certain alleles would be selectively lost during aging.

However, these considerations probably are quite simplistic, owing to the possibility that the scenario is much more complex. Indeed, unexpected nonmonotonic age-related trends of allele frequency can be found for genes related to survival and longevity. This is the case for the ApoB gene (De Benedictis et al. 1998), which we previously showed to be correlated with longevity (De Benedictis et al. 1997). We recently conceptualized these findings and created a model to account for the complex changes, with age, observed for ApoB gene allele frequencies (Yashin et al. 1998). According to this model, complex trajectories can be expected when the existence of "frail" and "robust" alleles of longevity-associated genes are assumed and when the mortality rates of the carriers of the two types of alleles are crossed. A similar conclusion was reached when changes, with age, in the allelic frequencies of genes related to cardiovascular risk factors, such as angiotensin-converting enzyme, were considered (Schachter et al. 1994).

As far as we know, the above-mentioned models (Toupance et al. 1998; Yashin et al. 1998) represent the only theoretical framework available to address the complex problems encountered when biodemographic data and genetic data, concerning longevity genes and genes related to risk factors for major age-related diseases, are merged and compared. A similar model for p53 could be of great interest and could help in (1) testing the hypothesis that the p53 Arg/Pro72 alleles are related to increased cancer risk and (2) answering the question of whether the frequency of the p53 alleles that we found in centenarians is compatible with this hypothesis. We predict that such a model will be quite difficult to develop, given that p53 is involved in a variety of tumors and that there is a relative paucity of data on p53 allele frequencies in people of different age groups and, particularly, in the elderly.

In this regard, if we admit that the data reported here imply no global differential chance of survival between p53 genotypes, our results could be due to compensatory effects. Indeed, opposite effects of genotypes on survival, at different ages, are predicted by the theory of negative, or antagonistic, pleiotropy (Williams 1957). The scenario is particularly interesting and challenging with regard to the healthy centenarians, who are the best models of successful aging and longevity and in whom a variety of other genetic and nongenetic risk factors for cardiovascular diseases was found (Mari et al. 1996; Mannucci et al. 1997; Baggio et al. 1998). Furthermore, healthy centenarians also can rely on other compensatory mechanisms, such as an effective and well-preserved immune system, to cope with internal and external threatening agents (Franceschi et al. 1995).

In conclusion, healthy centenarians may be considered useful models for testing basic theories on aging. Moreover, this selected group of healthy individuals will be useful for evaluating the impact of genetic risk factors on survival and longevity.

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