similar significant prolongations in normal quality-of-life parameters, such as physical symptoms, anxiety, and depression (all values $P<.04$, repeated-measures analysis of covariance) (*5*).

The above data, in conjunction with the meta-analysis presented by the authors, help us to define more clearly the potential survival advantages with the use of HAI in the treatment of patients with nonresectable liver metastases from colorectal cancer.

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References

(*1*) Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. Meta-Analysis Group In Cancer. J Natl Cancer Inst 1996;88:252-8.
(*2*) Takahashi K, Mori T, Takahashi T. Hepatic arterial infusion after hepatectomy for liver metastases of colorectal carcinoma to prevent residual hepatic recurrence. Gan To Kagaku Ryoho 1994;21:2165-8.
(*3*) Burke D, Earlam S, Fordy C, Allen-Mersh TG. Effect of aberrant hepatic arterial anatomy on tumour response to hepatic artery infusion of floxuridine for colorectal liver metastases. Br J Surg 1995;82:1098-100.
(*4*) Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases [*see* comment citation in Medline]. Lancet 1995; 344:1255-60.
(*5*) Zwinderman AH. Statistical analysis of longitudinal quality of life data with missing measurements. Qual Life Res 1992;1:219-24.

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Re: Telomerase Activity in Human Breast Tumors

Hiyama et al. (*1*) have recently investigated telomerase activity in human breast tumors. They examined 140 breast cancer specimens and found that stage classification exhibited the strongest association with telomerase activity.

Telomerase activity was detectable in all stage IV and in 96% of stage III cancers compared with 68% of stage I tumors, suggesting possible associations between telomerase activity and prognosis. However, follow-up data are required to address this issue. Hiyama et al. also suggested that telomerase reactivation is an important step in the progression of normal breast epithelial tissue to breast cancer, as was previously hypothesized (*2*). Since it is thought that ductal carcinoma in situ (DCIS) represents an intermediate step in the progression process to invasive cancer, it is important to investigate telomerase activity in DCIS lesions. Surprisingly, none of the 182 breast lesions that Hiyama et al. (*1*) studied were DCIS.

Hiyama et al. (*1*) were also able to detect telomerase activity in 14 samples obtained by fine-needle aspiration (FNA). All the 14 lesions were subsequently excised and were found to be invasive ductal carcinoma. This result is of great clinical importance and may increase the value of cytologic diagnosis. Since most DCIS lesions present as mammographic microcalcifications during breast screening, telomerase activity can be measured in samples obtained by stereotactic FNA of such nonpalpable lesions. Relationships of telomerase activity with histopathologic type and with other prognostic parameters such as c-erbB-2 should be investigated. Such an analysis will cast more light on the role of telomerase in breast carcinogenesis and on the natural history of DCIS.

Finally, the effects of tamoxifen on telomerase activity are worth investigating. This study could be carried out by performing a telomerase assay (TRAP—for telomeric repeat amplification protocol) (*3*) on breast cancers treated primarily with tamoxifen alone (core biopsy or FNA samples analyzed before and after treatment) or by adding tamoxifen directly to the tissue extract containing the enzyme.

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References

(*1*) Hiyama E, Gallahon L, Kataoka T, Kuroi K, Yokoyama T, Gazdar AF, et al. Telomerase activity in human breast tumors. J Natl Cancer Inst 1996;88:116-22.
(*2*) Shay JW, Wright WE, Werbin H Towards a molecular understanding of human breast cancer: a hypothesis. Breast Cancer Res Treat 1993;25:83-94.
(*3*) Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PL, et al. Specific association of human telomerase activity with immortal cells and cancer [*see* comment citation in Medline]. Science 1994;266:2011-5.

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Response

We appreciate the large amount of interest our work on telomerase activity in human breast cancer (*1*) has generated. We completely agree with the comments of Mokbel and Ghilchik about the need to examine earlier steps in progression to invasive breast cancer to determine if telomerase activity may be informative as a potential surrogate endpoint biomarker of cancer. Since telomerase activity is detected in preneoplasia in other diseases, it would not be surprising to detect telomerase activity in breast carcinoma in situ (CIS).

While additional studies are required to validate and extend our initial observations, we (*2*) and others (*3-5*) have recently obtained data directly addressing some of the issues raised. Both ductal (DCIS) and lobular (LCIS) carcinomas in situ have been examined. From David Tarin's laboratory, University of Oxford, U.K. (*4*), neither of two DCIS specimens examined had detectable telomerase activity. In contrast, Marcelo Aldaz's group at The University of Texas M. D. Anderson Cancer Center, Houston (*3*), demonstrated that

three of three DCIS specimens had telomerase activity. We have recently reported (*2*) that three of three LCIS specimens and one of one DCIS specimen had detectable telomerase activity. In addition, frozen sections of an LCIS (provided by Tom Frank, University of Michigan, Ann Arbor) had detectable telomerase activity. Some of the breast tumor specimens that we examined had mixtures of both invasive carcinoma and CIS. Nine of 11 carcinomas mixed with CIS were positive for telomerase activity. This observation suggests that at least two of these CIS specimens were negative for telomerase activity.

Overall, these results from several independent laboratories indicate that at least some breast CIS specimens have telomerase activity. While we believe that telomerase activity is reactivated and/or up-regulated (i.e., increased) during cancer progression and that this activity may be a new and independent prognostic indicator of the early onset of cancer, it is important to point out that we are still in the early stage of these investigations. We must await additional studies to determine if these findings can be replicated by other investigators. In addition, it is important to point out that breast CIS is a spectrum of diseases of varying prognostic and clinical importance. We hope that future analyses will shed light not only on the role of telomerase in breast carcinogenesis but also on the natural history of CIS.

We also agree with the comments of Mokbel and Ghilchik about the utility of stereotactic FNAs of nonpalpable breast lesions. In addition to FNA analysis, nipple aspirate fluids may provide a new and promising noninvasive method to screen women at risk for breast cancer for known prognostic markers, such as c-erbB-2, and putative markers, such as telomerase. Univariate and multivariate analyses of several prognostic indicators with telomerase activity in 400 stage II breast cancers showed a statistically significant correlation between telomerase activity and S phase, ploidy, and age at diagnosis (*5*).

The final point raised by Mokbel and Ghilchik on the effects of tamoxifen on telomerase activity in women who do not have surgery is an insightful comment. We have demonstrated that chemotherapeutic agents that resulted in differentiation of leukemia cells also inhibited telomerase activity (*6*).

We are currently exploring the effects of tamoxifen on telomerase expression in estrogen receptor-positive and estrogen receptor-negative breast cancer cell lines. Thus, knowledge of telomerase activity status in patients with cancer before and during therapy may have clinical utility for following disease progression and may predict early relapse of cancer.

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References

(*1*) Hiyama E, Gollahon L, Kataoka T, Kuroi K, Yokoyama T, Gazdar AF, et al. Telomerase activity in human breast tumors. J Natl Cancer Inst 1996;88:116-22.
(*2*) Pearson S, O'Neal N, Gollahon L, Piatyszek M, Fahey T, Shay JW. Telomerase activity in breast neoplasms. Soc Surg Oncol (abstr 19), 1996.
(*3*) Bednarek A, Sahin A, Aldaz CM. Telomerase in human breast cancer. Proc Am Assoc Cancer Res 1996;37:562 (abstr 3855).
(*4*) Sugino T, Yoshida K, Bolodeoku J, Tahara H, Buley I, Manek S, et al. Telomerase activity in human breast cancer and benign breast lesions: diagnostic applications in clinical specimens including fine needle aspirates. Int J Cancer. In press.
(*5*) Kim NW, Levitt D, Huang G, Wu F, Osborne K, Clark G. Correlation of telomerase with prognostic indicators of breast cancer. Proc Am Assoc Cancer Res 1996;37:562 (abstr 3852).
(*6*) Zhang W, Piatyszek MA, Estey E, Kobayashi T, Andreff M, Deisseroth AB, et al. Telomerase activity in acute myelogenous leukemia: inhibition of telomerase activity by differentiation-inducing agents. Clin Cancer Res 1996;2:799-803.

Note

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Re: Educational Attainment and Racial Differences in Cigarette Smoking

The brief communication by Escobedo et al. (*1*) regarding the relationship between education and smoking in different racial groups gives important direction to future tobacco control efforts. However, in reporting that Asian-Americans/Pacific Islanders (AAs/PIs) have the lowest smoking prevalence of any race/ethnic group (17%), the authors inadvertently reinforce the stereotype that AAs/PIs are a model minority with few health problems. More than 60 different ethnic groups make up the AA/PI category; 63% are foreign-born, and many do not speak English. The deceptively low AA/PI smoking prevalence figure reported by the authors can be attributed to several factors: 1) the National Health Interview Survey (NHIS), from which these data were derived, does not conduct interviews in any Asian language, thereby