Pergamon

European Journal of Cancer Vol. 33, No. 5, pp. 787–791, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00062-2

A Survey of Telomerase Activity in Human Cancer

J.W. Shay[1] and S. Bacchetti[2]

[1]Department of Cell Biology and Neuroscience, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235-9039, U.S.A.; and [2]Cancer Research Group, Department of Pathology, McMaster University Medical Center, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5

Research on the association of the ribonucleoprotein enzyme, telomerase, with human cancer has expanded rapidly in recent years. Essentially all major types of cancer have been screened and the presence of telomerase activity has been detected in the vast majority of cases. In this article we provide a summary, in table form, of the current data. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: survey, telomerase activity, human cancer, current literature

Eur J Cancer, Vol. 33, No. 5, pp. 787–791, 1997

INTRODUCTION

OVER ESSENTIALLY the last 2 years, screening of most types of human cancers has established a very strong association between the presence of telomerase activity and malignancy, making the enzyme one of the most common tumour markers ([1–3] and the articles in this Special Issue by N.W. Kim, pages 781–786; K.-F. Norrback and G. Roos, pages 774–780). Telomerase is a specialised reverse transcriptase that synthesises telomeric DNA and thus contributes to the maintenance of functional telomeres (see the article in this Special Issue by G.B. Morin, pages 750–760). In humans, telomerase activity in association with stable telomeres appears to be restricted to the germ-line and possibly to cycling stem cells in self-renewing somatic tissues (see articles by S.E. Holt *et al.*, pages 761–766; K.-F. Norrback and G. Roos, pages 774–780). More differentiated but proliferation competent somatic cells do not express detectable telomerase activity and indeed undergo progressive telomere shortening with cell division. In most cancers and in stem cells of renewal tissues, telomerase activity levels generally correlate with the proliferation state of the cells. The presence of the enzyme is almost always required for unlimited proliferation (immortality) whereas its absence may dictate a finite lifespan (senescence). Studies with experimentally transformed and immortalised human cells support this hypothesis (see article by T.M. Bryan and R.R. Reddel, pages 767–773).

Consequently, a requirement for telomerase in tumorigenesis is predicated on the assumption that tumour growth depends on, among other factors, the acquisition of the immortal phenotype by the malignant cells. This article summarises the current literature on the presence of telomerase in human tumours. Although the fast pace of research in this field may render the information rapidly outdated, we hope that the present survey of over 3500 tumour and control samples will aid basic researchers and clinical oncologists in evaluating the role of telomerase in cancer, and in designing future studies that will eventually determine the usefulness of the enzyme as a diagnostic or prognostic marker or as a target for cancer therapy.

We have restricted the data in the present article to papers that have been published or are in press up to December 1996 and have excluded abstracts and presentation at meetings. Cancers have been combined into tables according to tissue of origin or body site and, for most cancer types, results from several studies have been pooled. In the case of giant cell tumours of bone and of chordoma, the current availability of only single studies of very small size did not warrant presentation in a table format. Results in those studies indicated that telomerase activity was present in 5/5 giant cell tumours of bone [4] and 1/2 chordomas [5].

With very few exceptions, tumour samples were assayed by the PCR-based TRAP protocol ([6], also see article by N.W. Kim, pages 781–786). Since this assay detects telomerase activity in as few as 1–10 positive cells and 0.01% positive cells in a mixed population, the chances that tumour samples containing admixtures of normal and malignant cells would score as negative is greatly reduced. For this reason, negative samples from the few studies that used the less sensitive assay without PCR amplification of telomerase products, have been disregarded. As mentioned above, most normal somatic tissues lack detectable telomerase activity, making discrimination between positive and negative samples an easy task. In the case of cancers arising from normal tissues that express the enzyme, however, we considered positive only tumour samples that had telomerase levels significantly higher than the matched control tissue.

Correspondence to S. Bacchetti.

Samples for which relative levels of activity were not given have not been included. One caveat that pertains to tumour samples with very weak activity is the possible contamination with haematopoietic stem cells and inflammatory cells (e.g. activated lymphocytes), since these cells express low levels of the enzyme that may increase upon proliferation (see articles by S.E. Holt *et al.*, pages 761–766 and by K.-F. Norrback and G. Roos, pages 774–780). This latter fact also renders the issue of positive and negative haematological malignancies, such as leukaemias, the most difficult to resolve, since matched control samples are not available and basal levels of activity vary among individuals in an age-dependent manner.

The following ten tables summarise the current data on telomerase activity in various types of human cancer. The reader is advised to refer to the original articles for details and discussion.

Table 1. Head/neck and lung tissue

Pathology	No. positive/ No. tested	% positive	Ref.
Normal oral mucosa (or rinses)	1/39	(3)	[7,8]
Oral rinses from HNSCC*	14/44	(32)	[7]
Premalignant lesions	25/46	(54)	[7–9]
Head and neck squamous cell carcinoma	112/130	(86)	[3,7–10]
Non-small cell lung carcinoma	98/125	(78)	[11]
Small cell lung carcinoma	15/15	(100)	[3,11]
Adjacent tissue	3/68	(4)	[11]

*Head and neck squamous cell carcinoma.

Table 2. Gastrointestinal tract and pancreas

Pathology	No. positive/ No. tested	% positive	Ref.
Gastric metaplasia*/adenoma	4/15	(27)	[12]
Gastric carcinoma	72/85	(85)	[12,13]
Adjacent tissue	4/86	(5)	[12,13]
Colorectal adenoma*	20/44	(45)	[3,12,14,15]
Colorectal carcinoma†	123/138	(89)	[3,12,14–16]
Adjacent and normal tissues*	58/231	(25)	[3,12,14,17]
Benign pancreatic lesion‡	0/11	(0)	[18]
Pancreatic carcinoma	41/43	(95)	[18]
Adjacent tissue	5/36	(14)	[18]
Pancreatic brushings			
Benign	0/4	(0)	[18]
Carcinoma	8/8	(100)	

*Very weak activity relative to tumour samples, comparable to activity level in normal mucosa. Includes adenomatous polyps from familial adenomatous polyposis (FAP) patients, tubular adenomas, sporadic polyps with and without carcinoma. †Hereditary polyposis and non-polyposis cases, sporadic cases with and without mutator phenotype. ‡Cystadenoma, adenoma, cystic tumour, hyperplasia.

Table 3. Hepatic tissue

Pathology	No. positive/ No. tested	% positive	Ref.
Normal tissue	0/15	(0)	[19,20]
Non-malignant liver disease*	43/148	(29)	[19–22]
Hepatocellular carcinoma	149/173	(86)	[3,19–22]
Adjacent tissue	1/50	(2)	[19–22]

*Chronic/active hepatitis, cirrhosis; activity is very weak compared to carcinoma.

Table 4. Breast

Pathology	No. positive/No. tested	% positive	Ref.
Normal tissue	0/15	(0)	[3,23,24]
Breast fibrocystic disease	0/34	(0)	[24,25]
Breast fibroadenoma	11/40	(28)	[24–26]
Breast carcinoma *in situ*	9/12	(75)	[26,27]
Breast carcinoma (ductal and lobular)	300/339	(88)	[3,23–25]
Adjacent tissue	4/85	(5)	[24,25]
Breast FNA* benign	4†/47	(9)	[24,25]
Breast FNA malignant	26/32	(81)	[24,25]

*FNA, fine needle aspirates. †Positive samples from patients with fibroadenoma with Ki-67 positive ductal epithelia.

Table 5. Female reproductive tract

Pathology	No. positive/No. tested	% positive	Ref.
Ovary (fetal)	2/2	(100)	[3]
Ovary (adult)	1/3	(33)	[3,28]
Unfertilised egg	0/3	(0)	[29]
Normal myometrium/endometrium	0/18	(0)	[3,30]
Leiomyoma	0/14	(0)	[3,30]
Leiomyosarcoma	5/5	(100)	[3,30]
Endometrial adenocarcinoma	4/4	(100)	[30]
Cervical carcinoma	16/16	(100)	[30]
Vaginal carcinoma	3/3	(100)	[29]
Ovarian carcinoma	21/23	(91)	[28,30]

Table 6. Male reproductive tract

Pathology	No. positive/No. tested	% positive	Ref.
Testis (fetal/adult)	3/3	(100)	[3,29]
Mature spermatozoa	0/3	(0)	[29]
Normal prostate	0/43	(0)	[3,31,32]
BPH* without carcinoma	1/20	(5)	[3,32]
BPH with carcinoma	4/35	(11)	[31,32]
High grade PIN†	3/5	(60)	[3]
Prostate carcinoma	52/58	(90)	[3,31,32]

*Benign prostatic hyperplasia. † Prostatic intra-epithelial neoplasia.

Table 7. Kidney/urinary tract

Pathology	No. positive/No. tested	% positive	Ref.
Normal urothelium	0/45	(0)	[33–36]
Normal voided urine	3*/83	(4)	[35]
Dysplastic urothelium	3/7	(43)	[33–35]
Bladder carcinoma (all stages)	172/185	(92)	[33–36]
Bladder carcinoma (washings)	29/40	(73)	[34]
Bladder carcinoma (voided urine)	16/56	(29)	[34,35]
Renal carcinoma	95/115	(83)	[37,38]
Adjacent tissue	0/115	(0)	[37,38]
Wilms' tumour	6/6	(100)	[3]
Adjacent tissue	2/6	(33)	[3]

*Positive samples were from patients with benign prostatic hyperplasia.

Table 8. Neural tissue

Pathology	No. positive/ No. tested	% positive	Ref.
Normal retina/brain	0/9	(0)	[29,39,40]
Retinoblastoma*	17/34	(50)	[39]
Glioblastoma multiforme	45/60	(75)	[3,40,41]
Oligodendroglioma	19/19	(100)	[41]
Anaplastic astrocytoma	2/20	(10)	[41]
Meningioma			
Ordinary	5/30	(17)	
Atypical	12/13	(92)	[42]
Malignant	9/9	(100)	
Normal adrenal (newborn)	0/3	(0)	[43]
Ganglioneuroma	0.4	(0)	[43]
Neuroblastoma	99/105	(94)	[43]
Adjacent tissue	0/13	(0)	[43]

*Primary, unilateral or bilateral.

Table 9. Skin

Pathology	No. positive/ No. tested	% positive	Ref.
Normal epidermis	4/9*	(44)	[44]
Squamous cell carcinoma	15/18	(83)	[44]
Basal cell carcinoma	73/77	(95)	[44]
Melanoma	6/7	(86)	[44]

*Activity very weak compared to carcinoma.

*Table 10. Haematological tissues**

Pathology	No. positive/ No. tested	% positive	Ref.
Myeloma	1/1	(100)	[45]
Lymphoma			
Low grade	12/14	(86)	[45]
High grade	16/16	(100)	[45,46]
Lymph nodes, benign	5/15	(33)	[45]
Tonsils, benign	23/23	(100)	[45]
MDS	4/6	(67)	[47]
CML			
Chronic	30/42	(71)	[48–50]
Early accelerated	1/3	(33)	[48]
Blast	21/21	(100)	[49,50]
CLL			
Early	2/14	(14)	[47]
Late	4/7	(57)	[47]
APL	1/1	(100)	[48]
ALL	4/5	(80)	[48,49]
AML	47/64	(73)	[47,48,51]

*Data are for samples with activity above basal levels of normal peripheral blood or bone marrow (see text for discussion of telomerase activity in haematopoietic cells). MDS, myelodysplastic syndrome; CML, chronic myeloid leukaemia; CLL, chronic lymphoid leukaemia; APL, acute promyelocytic leukaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.

1. Bacchetti S, Counter CM. Telomeres and telomerase in human cancer. *Int J Oncol* 1995, **7**, 423–432.
2. Shay JW, Wright WE. Telomerase activity in human cancer. *Curr Opin Oncol* 1996, **8**, 66–71.
3. Kim NW, Piatyszek MA, Prowse KR, *et al.* Specific association of human telomerase activity with immortal cells and cancer. *Science* 1994, **266**, 2011–2015.
4. Schwartz HS, Juliao S, Sciadini M, Miller LK, Butler MG. Telomerase activity and oncogenesis in giant cell tumor of bone. *Cancer* 1995, **75**, 1094–1099.
5. Butler MG, Dahir GA, Hedges LK, Juliao SF, Sciadini MF, Schwartz HS. Cytogenetic, telomere, and telomerase studies in five surgically managed lumbosacral chordomas. *Cancer Genet Cytogenet* 1995, **85**, 51–57.
6. Holt SE, Norton JC, Wright WE, Shay JW. Comparison of the Telomeric Repeat Amplification Protocol (TRAP) to the new

TRAP-eze™ Telomerase Detection Kit. *Methods Cell Sci* 1996, **18**, 237–248.
7. Califano J, Ahrent S, Meininger G, Westra WH, Koch WM, Sidransky D. Detection of telomerase activity in oral rinses from head and neck squamous cell carcinoma patients. *Cancer Res* 1996, **56**, 5720–5722.
8. Mao L, El-Naggar AK, Fan Y-H, *et al.* Telomerase activity in head and neck squamous cell carcinoma and adjacent tissues. *Cancer Res* 1996, **56**, 5600–5604.
9. Mutirangura A, Supiyaphun P, Trirekapan S, *et al.* Telomerase activity in oral leukoplakia and head and neck squamous cell carcinoma. *Cancer Res* 1996, **56**, 3530–3533.
10. Hohaus S, Cavallo S, Bellacosa A, *et al.* Telomerase in human laryngeal squamous cell carcinoma. *Clin Cancer Res* 1996, **2**, 1895–1900.
11. Hiyama K, Hiyama E, Ishioka S, *et al.* Telomerase activity in small-cell and non-small-cell lung cancers. *J Natl Cancer Inst* 1995, **87**, 895–902.
12. Tahara H, Kuniyasu H, Yasui W, *et al.* Telomerase activity in gastric and colorectal carcinomas correlates well with malignant progression. *Clin Cancer Res* 1995, **1**, 1245–1251.
13. Hiyama E, Yokoyama T, Tatsumoto N, *et al.* Telomerase activity in gastric cancer. *Cancer Res* 1995, **55**, 3258–3262.
14. Chadeneau C, Hay K, Hirte HW, Gallinger S, Bacchetti S. Telomerase activity associated with acquisition of malignancy in human colorectal cancer. *Cancer Res* 1995, **55**, 2533–2536.
15. Li Z-H, Salovaara R, Aaltonen LA, Shibata D. Telomerase activity is commonly detected in hereditary nonpolyposis colorectal cancer. *Am J Pathol* 1996, **148**, 1075–1079.
16. Yoshida K, Sugino T, Goodison S, *et al.* Detection of telomerase activity in exfoliated cancer cells in colonic luminal washings and its related clinical implications. *Br J Cancer* 1997, in press.
17. Hiyama E, Hiyama K, Tatsumoto N, Shay JW, Yokoyama T. Telomerase activity in human intestine. *Int J Oncol* 1996, **9**, 453–458.
18. Hiyama E, Kodama T, Shimbara K, *et al.* Telomerase activity is detected in pancreatic cancer but not in benign pancreatic lesions. *Cancer Res* 1996, **57**, 326–331.
19. Miura N, Horkawa I, Suzuki M, *et al.* Progressive telomere shortening and telomerase reactivation during hepatocellular carcinoma. *Cancer Genet Cytogenet* 1997, in press.
20. Tahara H, Nakanishi T, Kitamoto M, *et al.* Telomerase activity in human liver tissues: correlation between chronic liver disease and hepatocellular carcinoma. *Cancer Res* 1995, **55**, 2734–2736.
21. Nouso K, Urabe Y, Higashi T, *et al.* Telomerase as a tool for the differential diagnosis of human hepatocellular carcinoma. *Cancer* 1996, **78**, 232–236.
22. Nakashio R, Kitamoto M, Tahara H, Nakanishi T, Ide T, Kajiyama G. Significance of telomerase activity in the diagnosis of small differentiated hepatocellular carcinoma. *Int J Cancer* 1997, in press.
23. Shay JW, Tomlinson G, Piatyszek MA, Gollahon LS. Spontaneous *in vitro* immortalization of breast epithelial cells from a Li–Fraumeni patient. *Mol Cell Biol* 1995, **15**, 425–432.
24. Sugino T, Yoshida K, Bolodeoku J, *et al.* Telomerase activity in human breast cancer and benign breast lesions: diagnostic applications in clinical specimens including fine needle aspirates. *Int J Cancer* 1996, **69**, 301–306.
25. Hiyama E, Gollahon L, Kataoka T, *et al.* Telomerase activity in human breast tumors. *J Natl Cancer Inst* 1996, **88**, 116–122.
26. Bednarek A, Sahin A, Brenner AJ, Johnston DA, Aldaz CM. Analysis of telomerase activity levels in breast cancer: positive detection at the *in situ* breast carcinoma stage. *Clin Cancer Res* 1997, **3**, 11–16.
27. Hiyama E, Gollahon L, Kataoka T, *et al.* Telomerase activity in human breast tumors (correspondence). *J Natl Cancer Inst* 1996, **88**, 839–840.
28. Counter CM, Hirte HW, Bacchetti S, Harley CB. Telomerase activity in human ovarian carcinoma. *Proc Natl Acad Sci USA* 1994, **91**, 2900–2904.
29. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. Telomerase activity in human germline and embryonic tissues and cells. *Dev Genet* 1996, **18**, 173–179.
30. Zheng P-S, Isawaka T, Yamasaki F, *et al.* Telomerase activity in gynecologic tumors. *Gynecol Oncol* 1997, in press.
31. Lin Y, Uemura H, Fujinami K, Hosaka M, Harada M, Kubota Y. Telomerase activity in primary prostate cancer. *J Urol* 1997, in press.
32. Sommerfeld HJ, Meeker AK, Piatyszek MA, Bova GS, Shay JW, Coffey DS. Telomerase activity: a prevalent marker of malignant human prostate tissue. *Cancer Res* 1996, **56**, 218–222.
33. Lin Y, Miyamoto H, Fujinami K, *et al.* Telomerase activity in human bladder cancer. *Clin Cancer Res* 1996, **2**, 929–932.
34. Muller M, Heine B, Heivappell R, *et al.* Telomerase activity in bladder cancer, bladder washings and in urine. *Int J Oncol* 1996, **19**, 1169–1173.
35. Yoshida K, Sugino T, Tahara H, *et al.* Telomerase activity in bladder carcinoma and its implications for non-invasive diagnosis by detection of exfoliated cancer cells in urine. *Cancer* 1997, **79**, 362–369.
36. Kamata S, Kageyama Y, Yonese J, Oshima H. Significant telomere reduction in human superficial transitional cell carcinoma. *Br J Urol* 1996, **78**, 704–708.
37. Mehle C, Piatyszek MA, Ljungberg B, Shay JW, Roos G. Telomerase activity in human renal cell carcinoma. *Oncogene* 1996, **13**, 161–166.
38. Fiedler W, Dahse R, Schlichter A, *et al.* Telomerase activity and telomere length in different areas of renal cell carcinoma. *Int J Oncol* 1996, **9**, 1227–1232.
39. Gupta J, Han LP, Wang P, Gallie BL, Bacchetti S. Development of retinoblastoma in the absence of telomerase activity. *J Natl Cancer Inst* 1996, **88**, 1152–1157.
40. Allsopp RC, Chang E, Kashhefi-Aazam M, *et al.* Telomere shortening associated with cell division *in vitro* and *in vivo*. *Exp Cell Res* 1995, **220**, 194–200.
41. Langford LA, Piatyszek MA, Xu R, Schold SC, Shay JW. Telomerase activity in human brain tumours. *Lancet* 1995, **346**, 1267–1268.
42. Langford LA, Piatyszek MA, Xu R, Schold SC, Wright WE, Shay JW. Telomerase activity: a prognostic indicator in ordinary meningiomas. *Human Pathol* 1997, in press.
43. Hiyama E, Hiyama K, Yokoyama T, Matsuura Y, Piatyszek MA, Shay JW. Correlating telomerase activity levels with human neuroblastoma outcomes. *Nature Med* 1995, **1**, 249–255.
44. Taylor RS, Ramirez RD, Ogoshi M, Chaffins M, Piatyszek MA, Shaw JW. Detection of telomerase activity in malignant and nonmalignant skin conditions. *J Invest Dermatol* 1996, **106**, 759–765.
45. Norrback KF, Dahlenborg K, Carlsson R, Roos G. Telomerase activation in normal B lymphocytes and non-Hodgkin's lymphomas. *Blood* 1996, **88**, 222–229.
46. Nilsson P, Mehle C, Roos R, Roos G. Telomerase activity *in vivo* in human malignant hematopoietic cells. *Oncogene* 1994, **9**, 3043–3048.
47. Counter CM, Gupta J, Harley CB, Leber B, Bacchetti S. Telomerase activity in normal leukocytes and in hematologic malignancies. *Blood* 1995, **85**, 2315–2320.
48. Broccoli D, Young JW, de Lange T. Telomerase activity in normal and malignant hematopoietic cells. *Proc Natl Acad Sci USA* 1995, **92**, 9082–9086.
49. Ohyashiki K, Ohyashiki JH, Iwama H, Hayashi S, Shay JW, Toyama K. Telomerase reactivation in leukemia cells. *Int J Oncol* 1996, **8**, 417–421.
50. Ohyashiki K, Ohyashiki JH, Iwama H, Hayashi S, Shay JW, Toyama K. Telomerase activity and cytogenetic changes in chronic myeloid leukemia with disease progression. *Leukemia* 1997, in press.
51. Zhang W, Piatyszek MA, Estey E, *et al.* Telomerase activity in acute myelogenous leukemia: inhibition of telomerase activity by differentiation-inducing agent. *Clin Cancer Res* 1996, **2**, 799–803.