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Review Article

Prevalence of Telomerase Activity in Human Cancer

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Telomerase activity has been measured in a wide variety of cancerous and non-cancerous tissue types, and the vast majority of clinical studies have shown a direct correlation between it and the presence of cancerous cells. Telomerase plays a key role in cellular immortality and tumorigenesis. Telomerase is activated in 80–90% of human carcinomas, but not in normal somatic cells, therefore, its detection holds promise as a diagnostic marker for cancer. Measurable levels of telomerase have been detected in malignant cells from various samples: tissue from gestational trophoblastic neoplasms; squamous carcinoma cells from oral rinses; lung carcinoma cells from bronchial washings; colorectal carcinoma cells from colonic luminal washings; bladder carcinoma cells from urine or bladder washings; and breast carcinoma or thyroid cancer cells from fine needle aspirations. Such clinical tests for telomerase can be useful as non-invasive and cost-effective methods for early detection and monitoring of cancer. In addition, telomerase activity has been shown to correlate with poor clinical outcome in late-stage diseases such as non-small cell lung cancer, colorectal cancer, and soft tissue sarcomas. In such cases, testing for telomerase activity can be used to identify patients with a poor prognosis and to select those who might benefit from adjuvant treatment. Our review of the latest medical advances in this field reveals that telomerase holds great promise as a biomarker for early cancer detection and monitoring, and has considerable potential as the basis for developing new anticancer therapies.

Key Words: biological tumor markers, cancer diagnosis, prognosis, telomere, telomerase

Telomeres are protective caps that function to contain unique hexameric repeats $(TTAGGG)_n$ at the ends of chromosomes, thought to be essential regulators of cell life span and chromosomal integrity.[1] Lagging strand DNA synthesis at the very end of chromosomes cannot be completed, which results in the progressive shortening of telomeric repeats with each round of division. This phenomenon is the so-called "end-replication problem".[2] Once telomeres have shortened to a critical length, cells undergo replicative senescence. For unlimited proliferation and genomic stability, cells need to compensate for the end-replication problem by using one of two known telomere-maintenance mechanisms: telomerase activation or alternative lengthening of telomeres.

Telomerase is a ribonucleoprotein enzyme complex that synthesizes telomeric repeats at the

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chromosomal ends. Telomerase has two essential components: an RNA subunit, called hTR (telomerase RNA),[3] which contains a template sequence on which the telomeric repeats are synthesized; and a protein, human telomerase reverse transcriptase (hTERT), which shows structural and functional similarities to viral reverse transcriptases.[4]

There are currently a number of methods used to detect telomerase activity. The telomeric repeat amplification protocol assay (TRAP), a method based upon a polymerase chain reaction (PCR), has been available since 1994, and has become the standard method for studying the diagnostic relevance of this enzyme.[1] Telomerase activity has also been specified qualitatively and quantitatively using modified TRAP assays; examples include TRAP–enzyme linked immunosorbent assay, the fluorescent TRAP assay, and the TRAP hybridization assay. Other methods have focused on the detection of the telomerase subunits, hTR and hTERT, using the reverse transcriptase PCR (RT-PCR) method. Real-time PCR methods have made possible the quantitative and reproducible determination of hTR and hTERT, whereas expression of the hTERT protein has been analyzed by immunocytochemistry using anti-hTERT monoclonal or polyclonal antibodies.

Telomere maintenance is regarded as an important mechanism by which tumor cells evade senescence, and in most cases, it is achieved by reactivating or upregulating telomerase activity. In fact, by using the highly sensitive methods mentioned above, various human cancers have been analyzed and a strong correlation has been shown to exist, both *in vitro* and *in vivo*, between telomerase activity and tumor malignancy. Kim et al[1] have demonstrated that telomerase activity can be detected in various solid tumors and in hematological malignancies. Furthermore, work in many laboratories worldwide has shown that telomerase is active in 80–90% of human cancers.[5] Although most normal somatic tissue lacks detectable telomerase activity, increasingly, the study-based analysis of primary human samples has revealed modest levels of telomerase activity in proliferative tissues with high renewal potential: for example, bone marrow, tissue from the gastrointestinal tract and uterine endometrium, and activated lymphocytes. Within these renewing tissues, telomerase is most active in the resident stem/progenitor cell compartments–particularly in early hematopoietic progenitor cells and in the gastrointestinal crypt epithelium.

Detecting Telomerase/hTERT in Clinical Samples of Human Malignant Tumors

During the process of carcinogenesis, telomerase is activated at different stages. In some instances, telomerase can be activated gradually throughout the progression of the cancer, whereas in other cases, this enzyme might already be ubiquitously expressed at the *in situ* or precancerous stage. These differences might affect the clinical utility of telomerase as a diagnostic marker or prognostic index. Early studies of telomerase activity in cancerous tissue were marked by the use of different approaches; different objectives were stipulated and several methods, both qualitative and quantitative, were used. Initially, most studies aimed at analyzing telomerase activity in cancerous bodies and the surrounding macroscopically healthy tissue. Later, the main objective of these studies was to verify whether telomerase activity could offer a reliable and non-invasive diagnostic or prognostic tool. More recent studies have focused on targeting telomerase as a novel form of cancer therapy.

One problem for the TRAP assay is that it is a solution-phase technique, thus, information about the cell type that expresses the telomerase is lost. Cancer cells, as well as some cells from healthy tissue and benign lesions (including germ cells, lymphocytes, stem or its progenitor cells, and certain epithelial cells) exhibit telomerase activity; therefore, it is not possible to know whether telomerase activity is coming from the tumor cells in the sample. To overcome this limitation, an *in situ* TRAP assay, which uses fluorescent dyes and microscopy to visualize telomerase activity in the nuclei of cells of interest, is needed to determine

whether telomerase expression is derived from normal telomerase-positive cells or from malignant cells. Another solution is to use quantitative TRAP or real-time PCR methods to define threshold values that can help distinguish cancer from normal tissue.

Telomerase is activated in 80–90% of human cancers. Telomerase expression is not usually detectable in somatic cells; therefore, its detection holds promise as a diagnostic tool for many types of carcinoma. In addition, telomerase is also activated in some premalignant tissue; thus, it is reasonable for physicians to expect that testing for telomerase activity is a useful method for the screening of high-risk patients. Hence, it is crucial to determine which cancers possess early robust telomerase activity and which manifest little to no telomerase activity, even in the most advanced stages of malignancy.

Expression of the hTR subunit has been found in all cells, regardless of the presence or absence of telomerase expression, although it is often amplified in cancer cells. However, hTERT expression correlates with telomerase activity because its presence is essential for enzymatic activity. Thus, detection of the *hTERT* mRNA is considered to be a more reliable marker of the presence of cancer cells in clinical samples. Our present article reviews the role of telomerase activation and its consequences with respect to clinical characteristics in relation to several types of human cancer. We also discuss the use of human telomerase and hTERT expression as diagnostic markers for the early detection of human cancer and/or as prognostic tools for predicting individual patient outcomes.

Breast

Normal mammary tissue does not exhibit detectable telomerase activity. In contrast, telomerase activity/hTERT expression has been detected in 75–90% of ductal carcinoma *in situ* lesions and in 90% of invasive breast cancers.[6–11] Yashima et al[12] have detected a link between a progressive increase in mean telomerase levels and an increase in the severity of histopathological change: a correlation of 14% in benign breast diseases, 92% in ductal carcinoma *in situ*, and 94% in invasive breast cancers. Although Sugino et al[7] and Nawaz et al[13] have found that there is no correlation between telomerase activity and tumor size or the occurrence of lymph node metastasis, Clark et al[14] have reported that telomerase activity is associated with a more aggressive tumor phenotype in patients with node-positive breast cancer. Recently, *hTERT* mRNA levels have been reported to be higher in patients who have recurrent disease or who have died from breast cancer, which suggests that the level of *hTERT* expression can be used as a prognostic marker.[15] (Table 1)

Fine-needle aspiration (FNA) biopsy of breast tissue is a minimally invasive sampling procedure with a proven value for achieving an initial

Table 1. Breast

Tissue	Positive ratio for telomerase activity % (positive/total number)			Reference
	Normal/adjacent tissue	Benign/premalignant lesion	Malignant lesion	
Breast cancer	4 (2/55)	45 (9/20)	93 (130/140)	[8]
	0 (0/6)	7 (1/15)	73 (52/71)	[7]
	0 (0/10)	20 (1/5)	95 (99/104)	[6]
	0 (0/13)	11 (1/9)	79 (22/28)	[13]
			75 (101/134)	[11][a]
FNA of breast		10 (3/29)	67 (10/15)	[7]
		56 (9/16)	90 (17/19)	[19]
		6 (5/85)	92 (80/87)	[16]

[a]*Detection of hTERT. FNA = fine-needle aspiration.*

evaluation of patients with palpable breast lesions. Many efforts have been made to assess the added value of testing for telomerase activity for the interpretation of breast FNA samples.[16] Approximately 10–40% of fibroadenoma tissue samples display low-level telomerase activity and hTERT expression, therefore, screening of FNA samples for telomerase/hTERT expression (with careful attention to benign diseases) is likely to become a powerful tool for the detection of breast cancer. However, even though the expression of telomerase in a highly suspicious breast FNA biopsy sample can upgrade the diagnosis to malignancy, a negative test result for telomerase cannot exclude the possibility of carcinoma.[17–19]

Lung

Telomerase activity has been demonstrated in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, as well as pulmonary sarcoma and mesothelioma.[20–27] The vast majority of NSCLCs display substantial telomerase activity: 62–94% of cases test positive (except for bronchioloalveolar carcinoma, which is telomerase positive in < 50% of cases).[22] SCLC is telomerase positive in 90–100% of cases, and expresses very high levels of enzyme activity. For NSCLC and SCLC, the presence of telomerase activity is correlated with poor survival, histological type, grade and smoking status.[23,28,29]

Several studies using NSCLC tissue samples have also reported that *hTERT* mRNA and hTERT protein are overexpressed in lung cancer biopsies when compared with normal lung tissue. However, the prognostic significance of hTERT expression or activity in NSCLC remains controversial. Although most studies have associated overexpression with poor prognosis,[28,30–33] others have failed to demonstrate any prognostic impact for this factor in NSCLC.[23,34,35] For example, Marchetti et al[28] have shown that, in stage I NSCLC patients, the *hTERT* expression levels are strongly correlated with reduced probability of survival. On the other hand, Lu et al[35] have not found a prognostic significance for *hTERT* mRNA expression in resected stage I NSCLC patients when performing a multivariate analysis of six molecular markers. However, Metzger et al[36] have recently demonstrated a survival benefit for patients with NSCLC who have high *hTERT* mRNA expression.

High levels of telomerase activity have been observed in specimens obtained by bronchoalveolar lavage, by bronchial washing, and by brushing tissue samples acquired during bronchofibroscopy.[37–41] The sensitivity and specificity of these tests for telomerase activity are 70–80% and 80–90%, respectively. Thus, the use of a cell-extract-based or an *in situ* TRAP assay, as complements to a cytological examination, might make the diagnosis of lung cancer more reliable.

Measurement of telomerase activity in sputum is a non-invasive method for the detection of lung cancer. However, in view of the lower-than-desired sensitivity of this test, sputum telomerase detection can be usefully combined with other biomarkers for early detection of lung cancer.[40,42]

For lung cancer that produces pleural effusion, testing for telomerase activity in these effusions has been shown to be a more sensitive tool than conventional cytology for the detection of malignant cells.[43–45] Positive telomerase activity suggests a more aggressive tumor and poorer prognosis. Moreover, telomerase activity could be a useful adjunct to cytological methods in the diagnosis of pleural micro-metastasis in patients with NSCLC. However, several groups have found telomerase activity is often observed in tuberculous pleural effusions.[46,47] That is, false-positive telomerase activity due to lymphocytic contamination might weaken the diagnostic value of telomerase activity in parts of the world where tuberculosis in endemic. (Table 2)

Digestive Organs: Stomach and Colon

Stomach

Although expression of telomerase activity and hTERT is generally more abundant in gastric cancer

Table 2. Lung

Tissue	Positive ratio for telomerase activity % (positive/total number)			Reference
	Normal/adjacent tissue	Benign/premalignant lesion	Malignant lesion	
NSCLC	4 (3/68)		78 (98/125)	[20]
			85 (84/99)	[21]
	0 (0/107)		62 (66/107)	[22]
	0 (0/115)		93 (107/115)	[23]
		0 (14/14)	71 (56/79)	[27]
	0 (0/14)		90 (62/69)	[36][b]
	0 (0/115)		94 (108/115)	[23][b]
SCLC			100 (11/11)	[20]
			93 (14/15)	[24]
Malignant pleural effusion of lung cancer[a]		8 (5/63)	83 (5/6)	[46]
		0 (0/32)	100 (11/11)	[45]
Bronchial wash or lavage			82 (18/22)	[38]
		29 (6/21)	78 (29/37)	[37]
		8 (1/13)	70 (16/23)	[39]
		10 (1/10)	68 (26/42)	[40]
		14 (1/7)	73 (16/22)	[41]
Sputum		0 (0/10)	82 (31/42)	[40]
		10 (3/30)	68 (23/34)	[42]

[a]Malignant pleural fluid has diagnosed by cytology; [b]Detection of hTERT. FNA = fine-needle aspiration; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

samples than in corresponding normal mucosa, there exists a significant overlap.[48–55] Consequently, the clinicopathological significance of telomerase activity in gastric cancer is controversial. Some studies have indicated that telomerase activity in gastric tumor tissue correlates well with tumor differentiation and depth of invasion,[56,57] whereas several other studies have shown no correlation between clinical or histological factors and telomerase activity.[50,52,54]

Telomerase activity in gastric lavage fluid is a sensitive potential tumor marker that might help increase the gastric cancer detection rate when combined with conventional cytopathological methods.[58] Telomerase expression has also been found in the peritoneal fluid of patients with gastric cancer.[59–61] In these studies, the presence of telomerase activity is associated with advanced stages of the disease or peritoneal metastasis.

Colon

The progression from normal or inflamed epithelium to the final stage of colorectal cancer involves morphological changes to precancerous dysplasia and adenomatous polyps. Many studies have revealed a detectable level of telomerase activity in normal mucosa.[62,63] In adenomatous polyps, telomerase activity is frequently present and is apparently connected to dysplasia grade and polyp size.[64] That is, although telomerase activity is overexpressed in colorectal carcinoma,[65–67] it cannot be used as a marker to screen patients with this malignancy. However, a high level of *hTERT* mRNA is associated with advanced stages, including metastatic colon carcinoma.[68]

Colorectal carcinoma is suggested as a serious sequela of inflammatory bowel diseases such as ulcerative colitis. However, Usselmann et al[69] have observed that, in all regions of the colon, when

Table 3. Stomach and colon

Tissue	Positive ratio for telomerase activity % (positive/total number)			Reference
	Normal/adjacent tissue	Benign/premalignant lesion	Malignant lesion	
Gastric cancer			85 (56/66)	[48]
	0 (0/20)	27 (4/15)	85 (17/20)	[49]
			89 (85/95)	[50]
		8 (1/12)	70 (7/10)	[51]
	0 (0/30)	38 (11/29)	93 (27/25)	[52]
	95 (41/43)		98 (42/43)	[54]
	62 (23/37)		90 (33/37)	[55][b]
Stomach lavage	0 (0/20)	28 (7/25)	80 (20/25)	[58]
Peritoneal washings[a]			50 (10/20)	[59]
			63 (20/32)	[60]
			100 (13/13)	[61]
Colorectal cancer	0 (0/50)	53 (16/30)	90 (45/50)	[65]
	14 (5/35)	50 (6/12)	92 (32/35)	[62]
	27 (3/11)	67 (14/21)	97 (33/34)	[63]
	0 (0/100)		96 (96/100)	[66]
			80 (98/122)	[67]
	45 (5/11)	57 (12/21)	94 (32/34)	[63][b]
Colon biopsy	0 (0/30)	50 (6/12)	88.5 (46/52)	[70]
Colon washing		0 (0/9)	60 (9/15)	[62]
	0 (0/11)		58 (11/19)	[71]
	0 (0/11)	0 (0/21)	62 (21/34)	[63]

[a]Clinically evident peritoneal metastases; [b]detection of hTERT. ESCC = esophageal squamous cell cancer.

compared to samples from normal individuals, there is a significantly reduced presence of telomerase activity in biopsies from patients with ulcerative colitis.

Telomerase activity and *hTERT* have been detected in small tissue samples from patients with colorectal carcinoma, including samples such as exfoliated cancer cells from colonic washings and colonic brush specimens.[62,63,70,71] The specificity of these tests is remarkable, but their sensitivity is relatively low. (Table 3)

Urinary Organs: Kidney and Bladder

Kidney

Telomerase activity is expressed in renal cell carcinoma less frequently than in other malignancies.[72–79] Furthermore, even when telomerase activity is found to be activated in renal tumor tissue, its expression is not related to clinicopathological parameters (histopathological grade, DNA ploidy, tumor stage, and clinical outcome).[72,73,78,80] That is, telomerase activity could be a potential marker for malignancy, but it is not suitable as a prognostic marker for renal cell carcinoma.

Bladder

Telomerase activity and hTERT are detected in about 90% of bladder cancers.[81–86] However, their presence is not specific to malignancy. A variable percentage of normal tissue from tumor-adjacent zones or from non-cancerous samples tests positive for telomerase. Some studies have found that the presence of telomerase activity or increased hTERT expression is associated with pathological grade and clinical stage of cancer.[81,86]

Testing for telomerase in exfoliated cells collected from urine or bladder washings seems a promising tool for the diagnosis and management of bladder cancer.[82,83,87–96] Urine samples can be collected easily, therefore, the ability to detect telomerase activity in urine samples could make telomerase a convenient diagnostic marker for this tumor. In fact, previous studies have shown that an assay of telomerase activity performed on voided urine is an important non-invasive tool for the diagnosis of bladder tumors, because this test has high sensitivity (46–92%) and specificity (66–95%) for even early-stage and low-grade tumors.[82,83,89–95] However, results from different studies have suggested that telomerase activity in urine is not related to tumor grade, size, or stage. The main limitation of this test is the rate of false-positive results due to the presence of inflammatory or non-tumor cells (i.e. epithelial cells from the lower genital tract), which can express telomerase activity.[87] As an alternative, the assessment of *hTERT* expression in urine represents a more sensitive and specific test for the detection of primary urothelial neoplasms than do tests for telomerase activity.[88,95,97] (Table 4)

Table 4. Kidney and bladder

Tissue	Positive ratio for telomerase activity % (positive/total number)			Reference
	Normal/adjacent tissue	Benign/premalignant lesion	Malignant lesion	
RCC	0 (0/56)		71 (40/56)	[72]
	17 (6/35)		74 (26/35)	[73]
	0 (0/21)		56 (28/50)	[74]
	0 (0/26)		82 (23/28)	[75]
	0 (0/52)	0 (0/8)	64 (28/44)	[76]
	0 (0/11)	17 (1/6)	60 (32/53)	[77]
	0 (0/30)		60 (18/30)	[78]
	16 (5/32)		86 (31/36)	[75][a]
	75 (15/20)		90 (18/20)	[79][a]
Bladder cancer	0 (0/7)	50 (1/2)	98 (39/40)	[81]
	0 (0/17)		86 (48/56)	[82]
	0 (0/37)		98 (41/42)	[83]
	0 (0/10)	0 (0/10)	100 (26/26)	[84]
	29 (4/14)	50 (2/4)	79 (11/14)	[85]
	0 (0/6)		100 (35/35)	[86][a]
Bladder washing	0 (0/12)		84 (36/43)	[83]
	4 (1/23)		96 (22/23)	[89]
		2 (2/86)	75 (62/82)	[96][a]
Urine	4 (3/83)		62 (16/26)	[82]
	0 (0/35)	34 (16/47)	85 (88/104)	[87]
	18 (9/50)		78 (42/54)	[90]
	9 (7/80)		46 (32/70)	[91]
	8 (6/79)		93 (112/121)	[92]
	12 (10/84)		90 (121/134)	[93]
	34 (49/144)		87 (59/68)	[94]
	0 (0/30)	24 (20/85)	75 (150/200)	[95]
	4 (1/26)		80 (26/33)	[97][a]
	0 (0/51)	5 (4/77)	92 (134/146)	[88][a]
	0 (0/30)	12 (10/85)	96 (192/200)	[95][a]

[a]*Detection of hTERT. RCC = renal cell cancer.*

Female Genital Organs: Uterus and Ovary

Uterus

Telomerase activity is found in almost all cancer tissue samples, as well as in most normal epithelial tissues samples from the uterus and the fallopian tubes of reproductive-age women.[98–100] With regard to the endometrium, telomerase activity is high during the proliferative phase of the menstrual cycle but suppressed during the secretory phase. Moreover, telomerase activity is rarely detected in postmenopausal women. These findings reflect the relationship between telomerase activity and features of the normal endometrium, which is regularly regenerated and has high proliferative activity. Thus, although telomerase activity is frequently detected in endometrial malignancies, a high frequency of telomerase positivity (up to 90%) has also been found in proliferative-phase endometrium.[99,101–104] The detection of telomerase in endometrial cancer is often not associated with architectural grade, myometrial invasion, or stage. However, although the presence of telomerase activity in the endometrium presents some difficulties for achieving a diagnosis and prognosis for cancer, the quantitative analysis of *hTERT* can have a role as a diagnostic or prognostic adjunct for patients with endometrial cancer.[105]

Cervical cancer evolves from pre-existing non-invasive premalignant lesions referred to as cervical intraepithelial neoplasia (CIN), graded CIN1 to CIN3. Elevated *hTERT* mRNA levels and telomerase activity can be detected in a marked subset of CIN3 lesions and > 90% of cervical carcinomas, whereas normal cervical tissue and low-grade CIN lesions only rarely show increased hTERT levels and telomerase activity.[98,103,106–111] According to a study by Kruse et al,[112] telomerase is not a prognostic marker in early CIN, because telomerase activity reflects a rather late step in the sequence from CIN3 to squamous cervical cancer. However, a connection between increasing hTERT expression and a trend toward greater severity of cervical lesions has been found by Tsezou et al[113] and Wisman et al.[114] In addition, Wang et al[115] have reported that the frequency of *hTERT* mRNA is related to the grade of CIN and cervical cancer.

Gestational trophoblastic disease refers to a category of neoplasm that includes complete hydatidiform mole, partial hydatidiform mole, and choriocarcinoma. All of these tumors are pregnancy-related and have proliferative neoplastic trophoblasts. Previously, we have found that telomerase activity is at its highest level during the early period of normal pregnancy and decreases significantly after the first trimester.[116] In addition, we have found that telomerase activity occurs in a similar fashion in placental tissue from normal early pregnancy and neoplastic trophoblastic tissue. Cheung et al[117] also have found that telomerase activity is present in choriocarcinoma as well as in early placental tissue and hydatidiform moles. The presence of telomerase activity in complete hydatidiform moles is also associated with the development of persistent gestational trophoblastic tumors (such as invasive moles and choriocarcinoma).[117,118] That is, proliferative normal and neoplastic trophoblasts possess similar levels of telomerase activity. However, there is a significant difference between the two: in normal pregnancy, telomerase activity is down-regulated over the course of gestation, whereas in hydatidiform mole, it is not.

Ovaries

Epithelial neoplasms of the ovary aggregate into three distinct clinicopathological groups: benign neoplasms confined to the ovary, cytologically malignant cancerous neoplasms, and an intermediate group referred to as borderline tumors or low-malignant-potential (LMP) tumors. The LMP tumors show significantly less aggressive behavior than classic epithelial ovarian carcinomas. Previous studies have reported telomerase activity in normal ovarian tissue and tumors, with the majority of frank ovarian carcinomas expressing telomerase activity.[99,103,119–124] However, studies of the rate of telomerase activity in benign and LMP ovarian tumors have produced mixed results. Wan et al[120] have reported that, although the majority of cystadenomas do not express

Table 5. Uterus and ovary

Tissue	Positive ratio for telomerase activity % (positive/total number)			Reference
	Normal/adjacent tissue	Benign/premalignant lesion	Malignant lesion	
Endometrial cancer	63 (5/8)		100 (6/6)	[103]
	89 (39/44)		100 (28/28)	[99]
	88 (15/17)			[102]
		100 (14/14)	95 (19/20)	[104]
	11 (1/9)		97 (35/36)	[100][a]
Cervical cancer		71 (5/7)	83 (10/12)	[98]
	0 (0/5)		100 (6/6)	[103]
	0 (0/5)		100 (16/16)	[106]
	0 (0/35)	29 (6/21)	92 (22/24)	[107]
	19 (3/16)	48 (29/61)	91 (21/23)	[108]
	7 (2/27)		92 (42/50)	[109]
	0 (0/8)		79 (85/107)	[110]
	13 (1/8)		80 (83/104)	[110][a]
	0 (0/20)	67 (29/43)	90 (36/40)	[111][a]
Cervical smear for cervical cancer	0 (0/10)	5 (1/22)	50 (1/2)	[103]
	0 (0/43)	69 (11/16)	97 (28/29)	[136]
	13 (7/88)	93 (51/55)	100 (59/59)	[137][a]
GTD	48 (53/111)	83 (15/18)	100 (3/3)	[116]
	34 (12/35)	31 (11/35)	100 (1/1)	[117]
	0 (0/4)	52 (16/31)	100 (5/5)	[118]
Ovarian cancer	0 (0/5)		92 (12/13)	[103]
		20 (2/10)	77 (24/31)	[119]
		21 (5/24)	100 (37/37)	[120]
	30 (3/10)	40 (6/15)	96 (24/25)	[99]
	33 (2/6)	31 (4/13)	74 (69/93)	[121]
		27 (3/11)	85 (22/26)	[122]
		36 (4/11)	88 (22/25)	[122][a]
	0 (0/12)	4 (1/28)	61 (20/33)	[123][a]
Peritoneal washings of ovarian cancer		5 (2/43)	64 (27/42)	[124]

[a]*Detection of hTERT. GTD = gestational trophoblastic disease.*

telomerase, all LMP tumors do express this enzyme. Oishi et al[125] have found that only 60% of LMP tumors are telomerase positive, whereas Yokoyama et al[99] have found that 40% of ovarian cystadenomas express telomerase activity. Thus, the detection of telomerase activity might be useful as an affiliated diagnostic procedure to help discriminate between malignant and benign tissue, but it should not be used in for pathological diagnosis.[126] However, *hTERT* expression might be a useful marker of patient response to platinum-based therapy during advanced stages of ovarian cancer.[126] (Table 5)

Sarcoma

Sarcoma cells have a relatively low level of telomerase expression compared to carcinoma cells. In fact, several types of sarcoma more commonly express alternative lengthening of telomeres and exhibit a markedly elongated telomere

Table 6. Sarcoma

Tissue	Positive ratio for telomerase activity % (positive/total number)			Reference
	Normal/adjacent tissue	Benign/premalignant lesion	Malignant lesion	
Liposarcoma		0 (0/4)	50 (6/12)	[130]
		0 (0/2)	86 (12/14)	[131]
		0 (0/11)	29 (4/14)	[132]
			63 (12/19)	[133]
			26 (9/34)	[129]
Malignant histiocytoma			22 (2/9)	[130]
		0 (0/2)	80 (8/10)	[131]
			67 (6/9)	[132]
Leiomyosarcoma			10 (1/10)	[130]
Rhabdomyosarcoma			50 (1/2)	[130]
Osteosarcoma			44 (31/71)	[128]
		23 (3/13)	58 (11/19)	[134]
			11 (1/9)	[135]
Chondrosarcoma			43 (3/7)	[134]
Ewing's sarcoma			43 (3/7)	[134]
			13 (1/8)	[135]

length.[127–129] The positive ratios of detectable telomerase are 10–86% in malignant soft-tissue tumors[129–133] and 11–58% in malignant bone tumors.[128,134,135] For example, the rate of telomerase expression in liposarcoma, malignant histiocytoma and chondrosarcoma samples is 26–86%, 22–80% and 11–44%, respectively. That is, according to different reports, the frequency of telomerase activity varies greatly among different sarcoma subtypes, which could be due to the homogeneous characteristics of sarcomas. Finally, although the expression of telomerase differs between sarcoma subtypes, some studies have reported that telomerase activity correlates with grade of malignancy.[130,132] (Table 6)

Conclusion

Telomerase activity has been measured in a wide variety of cancerous and non-cancerous tissues, and the vast majority of clinical studies have shown a direct association between telomerase activity and the presence of cancerous cells. Except for brain tumors, sarcomas, and some epithelial cancers, telomerase shows great promise as a biomarker for early cancer detection. In addition, telomerase activity has been shown to correlate with poor clinical outcome in late-stage NSCLC,[23,28,29] colorectal cancer,[68] and soft tissue sarcomas.[130,132] In such cases, testing for telomerase activity could be used to identify patients with poor prognosis and to select those who might benefit from adjuvant treatment. However, such testing is associated with several potential limitations and problems.

Measurable levels of telomerase have also been detected in carcinoma cells from various cytological samples: squamous carcinoma cells in oral rinses; lung carcinoma cells in bronchial washings; colorectal carcinoma cells in colonic luminal washings; bladder carcinoma cells in urine or bladder washings; and breast carcinoma and thyroid cancer cells in FNA biopsies. Such clinical tests for telomerase could be used as non-invasive and cost-effective methods for early detection and

monitoring of cancer. However, large cohort studies are required to statistically validate the association between these markers and cancer.

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