Telomerase Reverse Transcriptase Locus Polymorphisms and Cancer Risk: A Field Synopsis and Meta-analysis

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Abstract

Background

Several recent studies have provided evidence that polymorphisms in the telomerase reverse transcriptase (*TERT*) gene sequence are associated with cancer development, but a comprehensive synopsis is not available. We conducted a systematic review and meta-analysis of the available molecular epidemiology data regarding the association between *TERT* locus polymorphisms and predisposition to cancer.

Methods

A systematic review of the English literature was conducted by searching PubMed, Embase, Cancerlit, Google Scholar, and ISI Web of Knowledge databases for studies on associations between *TERT* locus polymorphisms and cancer risk. Random-effects meta-analysis was performed to pool per-allele odds ratios for *TERT* locus polymorphisms and risk of cancer, and between-study heterogeneity and potential bias sources (eg, publication and chasing bias) were assessed. Because the *TERT* locus includes the cleft lip and palate transmembrane 1-like (*CLPTM1L*) gene, which is in linkage disequilibrium with *TERT*, *CLPTM1L* polymorphisms were also analyzed. Cumulative evidence for polymorphisms with statistically significant associations was graded as "strong," "moderate," and "weak," according to the Venice criteria. The joint population attributable risk (PAR) was calculated for polymorphisms with strong evidence of association.

Results

Eighty-five studies enrolling 490,901 subjects and reporting on 494 allelic contrasts were retrieved. Data were available on 67 *TERT* locus polymorphisms and 24 tumor types, for a total of 221 unique combinations of polymorphisms and cancer types. Upon meta-analysis, a statistically significant association with the risk of any cancer type was found for 22 polymorphisms. Strong, moderate, and

weak cumulative evidence for association with at least one tumor type was demonstrated for 11, 9, and 14 polymorphisms, respectively. For lung cancer, which was the most studied tumor type, the estimated joint PAR for three polymorphisms (*TERT* rs2736100, intergenic rs4635969, and *CLPTM1L* rs402710) was 41%. Strong evidence for lack of association was identified for five polymorphisms in three tumor types.

Conclusions

To our knowledge, this is the largest collection of data for associations between *TERT* locus polymorphisms and cancer risk. Our findings support the hypothesis that genetic variability in this genomic region can modulate cancer susceptibility in humans.

Introduction

Human telomeres consist of repetitive *TTAGGG* DNA sequences that associate with a series of telomere binding proteins (shelterin complex) believed to provide genomic stability by protecting the linear chromosome ends from being recognized as DNA breaks to be repaired (1,2). The inability of the DNA replication machinery to copy the extreme ends of chromosomes, often referred to as the "end replication problem," is consistent with the observation that cells can lose telomeric repeats without initially affecting cell function (2). Thus, most human somatic cells show progressive telomere shortening with ongoing cell division until a subset of telomeres reach a critically shortened length and induce a DNA damage signal triggering a tumor protein p53 (TP53)-dependent G1/S cell cycle arrest referred to as replicative senescence. Thus, telomeres not only serve as chromosome "caps" to protect chromosome ends from being recognized as DNA damage, but also serve as a gauge for the mitotic (replication) age of a cell (1,2).

The gene encoding the enzyme telomerase reverse transcriptase (*TERT*), which synthesizes the *TTAGGG* DNA sequences onto the ends of chromosomes in cooperation with other proteins of the core telomerase complex (eg, telomerase RNA component [TERC] and dyskerin [DKC1]), is located on chromosome 5 (locus 5p15.33). With its activity, telomerase helps maintain the integrity of the genome in embryonic stem cells and in proliferating progenitor cells derived from quiescent normal stem cells (3,4). Telomerase is silent in the vast majority of human tissues and is only expressed in a small number of normal cell types such as dividing male germ-line spermatocytes and a subset of proliferating somatic adult stem cells (4).

In the early 1990s, investigators proposed a connection between telomeres, telomerase, aging, and cancer (5,6). The hypothesis was that most normal human cells lack telomerase activity and their telomeres shorten with each cell division, until they enter replicative senescence. Cells that lose critical cell-cycle checkpoint functions escape this initial growth arrest (replicative senescence) and continue to divide; cells that bypass senescence eventually enter a second growth arrest state (crisis) when many shortened chromosome ends fuse, leading to chromosome bridge-breakage-fusion

cycles, which almost universally result in apoptosis (5). In human cells, these two mechanisms to restrict cell growth (replicative senescence and crisis) are potent anticancer protection mechanisms. Most human cells remain in this crisis period with cell growth being balanced by cell death until a rare cell acquires a mechanism, such as telomerase expression, that can maintain or lengthen telomeres. Cells that have escaped crisis generally have two defining hallmarks, telomere stability and reactivation of telomerase; this rare cell type that can maintain telomeres is then able to grow continuously (ie, becomes immortal), and this is generally believed to be a critical step in cancer progression (5).

In the light of the already abundant evidence linking telomerase activity to the development of many tumor types, many researchers are devising a variety of methods to target telomerase as a novel therapeutic approach potentially useful in a range of cancers (7,8); moreover, other investigators are testing the hypothesis that variability of the *TERT* gene sequence might be a general mechanism affecting individual cancer predisposition (9). Regarding the latter field of investigation, tens of thousands of patients affected with different cancer histotypes have been so far enrolled in molecular epidemiology studies and some *TERT* polymorphisms have been reported to be associated with cancer risk, although findings are not always concordant (9). Because there is no synopsis available on this subject, we systematically reviewed the data published to date on the relationship between *TERT* locus polymorphisms and cancer risk, and quantitatively summarized the available evidence by performing a formal meta-analysis.

Materials and Methods

Search Strategy, Eligibility Criteria, and Data Extraction

We followed the methods proposed by the Human Genome Epidemiology Network (HuGENet) (10) as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) (11) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (12). A two-step search strategy was adopted. First, a systematic review of original articles, reviews and meta-analyses analyzing the association between *TERT* locus polymorphisms and cancer risk was performed by searching PubMed, Embase, Cancerlit, Google Scholar, and ISI Web of Knowledge databases (Supplementary Figure 1, available online). The search included the following keywords: "cancer", "tumor", "carcinoma", "melanoma", "sarcoma", "lymphoma", "leukemia", "polymorphism", "SNP", "variant", "risk", "association", "TERT", "telomerase", "locus", "5p15.33" and "gene". The 5'-end of *TERT* resides in a 62 Kb region of high linkage disequilibrium (LD) that encompasses the upstream gene cleft lip and palate transmembrane 1-like (*CLPTM1L*) (9) (Supplementary Figure 2, available online). Therefore, polymorphisms not belonging to the *TERT* gene but localizing within this LD area might be tagging relevant *TERT* polymorphisms; accordingly, *CLPTM1L* was used as an additional search term in the second step. Finally, in the light of the growing diffusion of high-throughput technological platforms for the investigation of gene polymorphisms, the expression "genome wide association study" and its acronym "GWAS" were also used as key words. In order to retrieve other potentially relevant data, we then performed the following: 1) the name or identity of each polymorphism was used as a keyword to further refine the search; 2) cited references from selected articles were reviewed; 3) publicly available databases dedicated to associations between genotype and phenotype (eg, Database of Genotypes and Phenotypes [dbGaP], http://www.ncbi.nlm.nih.gov/gap) were searched; 4) authors were contacted whenever unreported data were potentially useful for the systematic review or to rule out overlapping data reported in different publications.

Studies dealing with the association between any *TERT* locus polymorphism and predisposition to any type of cancer in humans were considered eligible, provided that the raw or summary data necessary to calculate the risks were available. Exclusion criteria were non-English language and data published in abstract form. For each polymorphism, exclusion criteria were less

than 5% minor allele frequency (MAF) in control subjects (rare polymorphisms) and violation of Hardy-Weinberg equilibrium (HWE).

The following data were extracted from eligible studies: authors' names; region or country where the study was conducted; year of publication; number of case subjects with cancer and healthy control subjects; ethnicity; allelic frequency in both case subjects and control subjects (if no raw data were available, summary data were collected; ie, odds ratios [ORs] and 95% confidence intervals [CIs]); MAF and HWE in control subjects; study design, genotyping, and statistical methods. For analysis purposes, the database, which will be updated on a yearly basis and will be publicly available on the Melanoma Molecular Map Project website [(13); http://www.mmmp.org], was frozen in April 2011. Data were extracted independently by the two investigators (DV and SM) in order to ensure homogeneity of data collection and to rule out the effect of subjectivity in data gathering and entry. Disagreements were resolved by iteration, discussion, and consensus. To unravel potential systematic biases, a third investigator (DN) performed a concordance study by independently reviewing all eligible studies; complete concordance (100%) was reached for all variables assessed.

Statistical Analysis

Meta-analysis. Because all the investigated gene variants were biallelic polymorphisms, per-allele odds ratios and corresponding 95% confidence intervals were used to assess the strength of association between each genetic variant and cancer risk, where protective and risk alleles were associated with ORs less than or greater than 1, respectively. Per-allele ORs were calculated for each study and each polymorphism, assuming a co-dominant genetic model. This assumption was suggested by the following reasons: 1) for some studies (including many GWAS), neither raw nor summary genotype data were available (only per-allele ORs were reported, which only allows to explore the co-dominant model); 2) the co-dominant model is widely used as a conservative choice between the recessive and dominant models, and 3) it does not require adjustment for multiple

hypotheses (which is necessary when different models are tested); 4) methods that let the data dictate the genetic model (ie, model-free approach) require raw data on genotype distributions (which were not available for many identified studies).

For each allelic contrast (ie, data regarding a specific polymorphism and a given tumor type), summary per-allele ORs (meta-risks) were calculated by performing random-effects meta-analysis as per Der Simonian and Laird (ie, using the inverse variance method to weight the studies), a Z test being used to formally prove the statistical significance. The choice of the random-effects model was suggested by two main reasons: 1) the variety of histological cancer types, which was far from being fully represented for each genetic variant; 2) because the Q test for between-study heterogeneity is characterized by low statistical power, which is especially relevant when few studies are available; 3) in general, the random-effects model is a more conservative choice when heterogeneity is present, whereas it reduces to the fixed-effect model when heterogeneity is absent.

For each polymorphism (whose allele of interest is indicated by the corresponding nucleotide letter in squared brackets), a meta-analysis was performed if at least two data sources were available. Stratification by ethnicity and histological subtype was done if data permitted. When a publication reported the data in an ancestry-specific way, each ancestral subset was considered as a distinct study. Similarly, with regard to GWAS, if data were available, discovery (hypothesis testing) and replication (validation) phases were considered as separate studies.

Meta-analysis also included evaluation of between-study heterogeneity, sensitivity analysis, and examination for bias. Heterogeneity (true variance of effect size across studies) was formally investigated using a Q test (to assess whether observed variance exceeds expected variance) and I^2 statistic (it indicates the percentage of the variability in effect estimates because of true heterogeneity rather than sampling error) (14). The Q test for heterogeneity was also used to formally compare effects (ie, meta-risk) between groups of interest (eg, different ethnicities).

The extent to which the combined risk estimate might be affected by individual studies was assessed by consecutively omitting every study from the meta-analysis (leave-one-out sensitivity

analysis). This approach would also capture the effect of the oldest or first positive study (first study effect).

Funnel plot was used to detect the so-called "small study effect." Publication and selection biases in meta-analysis are more likely to affect small studies, which also tend to be of lower methodological quality (15). Funnel plot asymmetry was formally investigated with the Egger linear regression approach (Egger's test) and the Begg rank correlation test (Begg's test). The impact of small study effect bias on the summary effects was formally assessed by means of the trim-and-fill method described by Duval and Tweedie (16). The excess of statistically significant findings (potentially indicating the so-called "chasing bias") was evaluated by the test proposed by Ioannidis and Trikalinos (Ioannidis and Trikalinos test) (17).

The population attributable risk (PAR) was calculated using the following formula:

$Pr\ (RR - 1) / [1 + Pr\ (RR - 1)]$, where *Pr* is the proportion of control subjects exposed to the allele of interest and the relative risk (*RR*) was estimated using the summary estimates (ORs) calculated by the meta-analysis. The joint PAR for combinations of polymorphisms was calculated as follows: $1 - (\prod_{1 \to n} [1 - PAR_i])$, where PAR_i corresponds to the individual PAR of the *i*th polymorphism and *n* is the number of polymorphisms considered (18). Because PAR is a relative measure of effect and thus it does not account for the absolute risk of disease, we also calculated the attributable community risk (ACR), according to the following formula: $(I_c - I_0)/I_c$, where I_c is the crude risk in the general population (probability of developing the disease during the entire lifetime) and I_0 is the risk of disease in non-exposed (ie, in people carrying the protective allele) (19).

P values less than .05 were considered statistically significant for all tests, except for Q test for heterogeneity, Egger's test, Begg's test and Ioannidis and Trikalinos test, for which a less stringent 10% alpha level of statistical significance was applied. The latter three tests were performed if at least four studies were available. All tests were two-sided. The Bonferroni method was used for *P* value adjustment in case of multiple testing. Statistical analyses were performed with STATA 11.0/SE software (College Station, TX, USA).

***Assessment of cumulative evidence*.** In order to evaluate the epidemiological credibility of each statistically significant association identified by meta-analysis, we used the Venice criteria (10,20). Briefly, credibility was defined as "strong," "moderate" or "weak" based on grades A, B or C in three categories: 1) amount of evidence, 2) replication of the association, and 3) protection from bias. Amount of evidence (which roughly depends upon the study sample size) was graded by the sum of test allele among case and control subjects in the meta-analysis: grades A, B or C were assigned for values greater than 1000, 100–1000 and less than 100, respectively. Replication was graded by the heterogeneity statistic: grades A, B, and C were assigned for I^2 less than 25%, 25–50%, and greater than 50%, respectively. Protection from bias was graded as grade A if there was no observable bias (bias was unlikely to explain the presence of the association), grade B if bias could be present, or grade C if bias was evident. Assessment of protection from bias also considered the magnitude of association: a grade "C" was assigned to an association with a summary OR less than 1.15, or greater than 0.85 in case of protective effect.

Overall, the cumulative epidemiological evidence for statistically significant associations upon meta-analysis were considered to be "strong" if all three grades were A, "weak" if any grade was C, and "moderate" in all other cases. In case of no statistically significant association upon meta-analysis, the minimum detectable risk was calculated considering a hypothetical study with sample size equal to the combined sample sizes of the studies reporting on a given polymorphism (error alpha and power were set at 5% and 90%, respectively). If no heterogeneity was found (I^2 <25% and Q test P >.10) and the detectable alternative included non-negligible associations (ie, OR ≥1.15 or ≤0.87), we considered the cumulative evidence sufficient to rule out any meaningful relationship between that polymorphism and cancer risk (strong evidence); in the other cases the evidence for lack of association was considered weak (ie, more data are necessary before the association can be ruled out).

Results

Literature Search

We found 6,497 potentially relevant articles, and retrieved 66 articles (18,21-84) reporting on 85 case–control studies that assessed the association between *TERT* locus polymorphisms and cancer risk, and met the eligibility criteria (Supplementary Figure 1, available online). They were published in a relatively limited time span (2003–2011), witnessing the recent interest in this molecular epidemiology field. We identified 494 allelic contrasts after including ethnicity and tumor subtype specific data, whose details are reported in Supplementary Table 1, available online. Overall, data were available on 67 polymorphisms and 24 tumor types, with 490,901 subjects being genotyped (195,305 case subjects and 295,596 control subjects): the 221 unique combinations of *TERT* locus polymorphisms with cancer types are depicted in a heat-map (Supplementary Figure 3, available online), which also includes information on number of studies, type of association (statistically significant vs non-statistically significant), and the level of evidence (strong, moderate, and weak) for association. Considering the total number of case and control subjects enrolled in the eligible studies, *TERT* locus polymorphisms were most frequently investigated in lung cancer (56,682 subjects; 29.0%), the only tumor type for which data on histological subtypes could be included in the meta-analysis; the other five most frequently studied tumor types were prostate (47,294 subjects; 24.2%), colon (16,279 subjects; 8.3%), breast (15,090 subjects; 7.7%) and bladder (10,202 subjects; 5.2%) carcinomas, and central nervous system (CNS) tumors (8,795 subjects; 4.5%).

The median number of subjects enrolled per study was 2,771 (range: 125–79,600). White subjects of European ancestry was by far most frequently involved (425,010 subjects; 86.5%), Asian ethnicity representing virtually all the remaining subjects. In the majority of the studies (58 of 85), selected *TERT* locus polymorphisms were investigated, whereas the remaining 27 were GWAS. All variants were single-nucleotide polymorphism (SNP), except for two minisatellite polymorphisms (*TERT* MNS16a and VNTR2-2nd) and one deletion (*TERT* Glu441del).

Among the 485 allelic contrasts for which an OR could be calculated, 233 (48%) showed a statistically significant association with risk of cancer (Supplementary Table 1, available online). Available data enabled us to perform 118 meta-analyses (including 41 subgroup analyses based on specific ancestries and histological subtypes) for 35 polymorphisms tested in one or more different tumor types and for which at least two studies were available. The main findings of these meta-analyses reporting 75 (64%) statistically significant associations and 43 (36%) non-statistically significant associations between *TERT* locus polymorphisms and cancer, are shown in Table 1 and Table 2, respectively.

Overall, 22 polymorphisms were associated with the risk of developing one or more types of cancer, but only 11 showed strong cumulative evidence according to the international guidelines known as Venice criteria (moderate and weak cumulative evidence was found for 9 and 14 polymorphisms, respectively). In particular, among the 75 allelic contrasts for which the meta-analysis showed statistically significant associations with cancer risk, the cumulative evidence was strong, moderate, and weak for 20 (27%), 15 (20%), and 40 (53%) allelic contrasts, respectively. The results for polymorphisms with strong evidence of an association with at least one tumor type are described below. Findings for each polymorphism are detailed in the Supplementary Results, available online. Finally, for five of the 43 meta-analyses (12%) that showed no statistically significant association, the cumulative evidence for lack of association with cancer risk was strong.

Associations between *TERT* locus Polymorphisms and Cancer Risk

***rs2736098*.** Although rs2736098 is a synonymous polymorphism (*G>A*; Ala305Ala), this *TERT* SNP has been shown to be associated with telomere length, but not with *TERT* expression (41). On the other hand, rs2736098 is in linkage disequilibrium (LD) with rs2853669 (pairwise correlation coefficient r^2 = 0.79) (24), a SNP granted functional relevance (*see* Supplementary Results,

available online). Therefore, rs2736098 may simply be a marker tagging the relevant polymorphism.

Meta-analysis by tumor type revealed a statistically significant association between the minor allele rs2736098[*A*] and both lung (OR = 1.21, 95% CI = 1.15 to 1.27) and bladder cancer (OR=1.19, 95% CI = 1.12 to 1.25) (Table 1). According to the Venice criteria, the cumulative evidence for the association between rs2736098[*A*] and the risk of these two tumor types was strong. Because the minor allele frequency (MAF) of rs2736098 was 26%, the estimated population attributable risk (PAR) for lung and bladder cancer was 6% and 5%, respectively. Meta-analysis of available data showed no association between this SNP and either prostate cancer or central nervous system (CNS) tumors (Table 2).

rs2736100. SNP rs2736100 is located in intron 2 of *TERT* and, on the basis of the Evolutionary and Sequence Pattern Extraction through Reduced Representation (ESPERR) score (85), is located within a putative regulatory region (40). This polymorphism has also been linked to idiopathic pulmonary fibrosis, a disease associated with increased risk of developing lung cancer (86). It is also the most studied polymorphism of the *TERT* gene, as it was described in 46 studies enrolling 74,785 case subjects with 11 tumor types and 115,726 control subjects.

Thirty two studies reported a statistically significant association between the minor allele rs2736100[*C*] and cancer susceptibility. Notably, for testicular cancer, this allele was associated with a decreased disease risk, whereas for all other tumor types it was associated with an increased disease risk. Upon meta-analysis, the association between this *TERT* polymorphism and cancer risk was statistically significant for lung, bladder, pancreatic, testis, and CNS tumors (Table 1), but not melanoma (data for melanoma is presented in Table 2). Lung cancer was by far the most studied tumor type, with 50,917 case subjects and 72,598 control subjects enrolled in 23 studies. The meta-risk was highly statistically significant (OR =1.19, 95% CI = 1.14 to 1.23), but with a large amount of heterogeneity (I^2 = 77%, P < .001), which made the cumulative evidence for association weak. A

stronger association was noted in Asians (OR = 1.26, 95% CI = 1.20 to 1.32) compared with whites (OR = 1.11, 95% CI = 1.08 to 1.15; $P_{heterogeneity}$ for difference between ORs < .001); however, the cumulative evidence remained weak for both ancestries because of the small overall association among whites and the large heterogeneity (I^2 = 68%, P < .001) coupled with potential chasing bias (Ioannidis and Trikalinos test P = .035) among Asian studies.

Beacuse data were permissive, we investigated this SNP also in relation with lung cancer subtypes. The risk of adenocarcinoma was highest among all subtypes (OR = 1.30, 95% CI = 1.25 to 1.36), but again, the cumulative evidence was weak as a result of lack of replication and large heterogeneity (I^2 = 62%, P = .001). However, when ethnicity was taken into account, the risk among whites was highly statistically significant (OR = 1.22, 95% CI = 1.17 to 1.27) and the cumulative evidence was strong (estimated PAR = 11%, MAF = 45%). The association of rs2736100 with adenocarcinoma was reported to be stronger among never smokers (65), a population subset where this is the most common form of lung cancer. Moreover, the estimated joint PAR for three polymorphisms including *TERT* rs2736100, intergenic rs4635969, and *CLPTM1L* rs402710) was 41% (Figure 1). Among Asians, the meta-risk for this tumor subtype was higher (OR = 1.35, 95% CI = 1.29 to 1.42, $P_{heterogeneity}$ <.001) but heterogeneity remained statistically significant (I^2 = 47%, P = .067) and the cumulative evidence for association was moderate.

For squamous cell carcinoma, the meta-risk point estimate was small for rs2736100[*C*] (OR = 1.06, 95% CI = 1.01 to 1.12) and the cumulative evidence for association was weak. For small cell lung cancer (SCLC), the cumulative evidence for lack of association (OR=1.05, 95% CI = 0.99 to 1.09) was strong (Table 2). Other subgroup analyses performed for lung cancer are reported in Table 1.

rs2736100[*C*] was statistically significantly associated with reduced risk of testicular germ cell carcinoma (TGCC) (OR= 0.75, 95% CI = 0.70 to 0.81), the cumulative evidence for association was strong (estimated PAR for the risk allele rs2736100[*A*] = 22%,risk allele frequency = 55%).

For other tumor types, no strong evidence could be demonstrated. For pancreatic cancer, the available data were in favor of a small risk increase (OR = 1.12, 95% CI = 1.04 to 1.20) and the cumulative evidence was weak. The association of rs2736100[*C*] with the risk of bladder carcinoma was also statistically significant (OR = 1.19, 95% CI = 1.05 to 1.34), but because of the relatively low number of subjects enrolled (100<*n*<1000, *n*= subjects carrying the minor allele), the cumulative evidence was moderate. Finally, the association with risk of CNS tumors was even stronger (OR = 1.34, 95% CI = 1.22 to 1.46), but the cumulative evidence for association was weak as a result of large heterogeneity (I^2 = 60%, *P* = .02).

rs2853676. The association of this *TERT* intronic polymorphism with risk of cancer was evaluated in 18 studies, including 31,481 case subjects (11 tumor types) and 44,122 control subjects. Four studies on CNS tumors and one on cutaneous melanoma reported a statistically significantly increased risk for carriers of the minor allele (*A*), whereas one study described a reduced risk for TGCC. Meta-analysis by tumor type revealed a strong association between rs2853676[*A*] and increased risk of CNS tumors (OR = 1.26, 95% CI = 1.21 to 1.32), and the cumulative evidence was strong (estimated PAR = 7%, MAF = 24%).

In contrast, the cumulative evidence for lung cancer risk was weak, because of a small meta-risk (OR=1.06, 95% CI = 1.01 to 1.10). Finally, no association could be demonstrated for pancreatic cancer (OR = 0.93, 95% CI = 0.86 to 1.00) and melanoma (OR = 1.16, 95% CI = 0.81 to 1.66).

rs31489. This intronic SNP of the *CLPTM1L* gene was chosen because it is located in a DNA region in LD with the *TERT* promoter and the 5'-end of *TERT* gene (Supplementary Figure 1, available online) (9). Nine studies reported statistically significant association between cancer risk and the minor allele (*A*), but with opposite risk directions for lung cancer and skin basal cell carcinoma (BCC) (decreased) as compared to pancreatic cancer and TGCC (increased).

Meta-analysis by tumor type confirmed that rs31489[*A*] is associated with an increased risk of pancreatic cancer (OR = 1.18, 95% CI = 1.06 to 1.32) and TGCC (OR = 1.28, 95% CI = 1.16 to 1.41) but is statistically significantly associated with reduced risk of lung cancer (OR = 0.83, 95% CI = 0.78 to 0.88) (Table 1). The cumulative evidence for association was strong only for testicular cancer (estimated PAR = 11%, MAF = 36%). For the other tumor types no meta-analysis could be performed.

rs380286. This SNP is located in an intronic region of *CLPTM1L*. Two studies reported that subjects carrying the minor allele (*A*) were associated with reduced risk of lung cancer (OR = 0.85, 95% CI = 0.80 to 0.91), and the cumulative evidence was strong (estimated PAR for risk allele rs380286[*G*] = 13%, major allele frequency = 63%) (note that in this case the "risk" allele coincides with the "major" allele).

rs401681. This SNP is located in an intronic region of *CLPTM1L*. Like rs2736098, rs401681 was reported to be associated with telomere length (but not TERT expression) (41), which supports its relevance for telomere biology and potentially cancer development. At present rs401681 is the most widely studied *TERT* locus polymorphism, because it was assessed for cancer risk in 56 series enrolling 89,903 case subjects (23 tumor types) and 155,202 control subjects (Supplementary Table 1, available online). In 29 studies a statistically significant association was observed between the minor allele (*T*) and cancer risk; however, 21 studies described a decreased cancer risk whereas eight described an increased risk.

Meta-analysis by cancer type revealed that rs401681[*T*] carriers have a modestly increased risk of pancreatic carcinoma (OR = 1.14, 95% CI = 1.01 to 1.29) and skin melanoma (OR = 1.12, 95% CI = 1.03 to 1.22). Conversely, a modest risk reduction was observed for bladder (OR = 0.89, 95% CI = 0.86 to 0.92), lung (OR = 0.87, 95% CI = 0.84 to 0.89) and prostate (OR = 0.92, 95% CI = 0.89 to 0.95) cancer and skin squamous cell carcinoma (SCC) (OR = 0.92, 95% CI = 0.84 to 0.99). Finally,

a more pronounced risk reduction was detected for BCC (OR = 0.82, 95% CI = 0.76 to 0.89). In no case was the cumulative evidence strong because of between-study heterogeneity and/or small overall association (Table 1).

For lung cancer, available data also enabled us to perform meta-analysis by ancestry and histological subtype. SNP rs401681[*T*] was associated with statistically significantly reduced risk of both adenocarcinoma (OR = 0.87, 95% CI = 0.81 to 0.93) and SCC (OR = 0.85, 95% CI = 0.76 to 0.96), but not with SCLC (OR = 0.98, 95% CI = 0.90 to 1.07). Nevertheless, the cumulative evidence for the first two lung cancer subtypes was weak because of heterogeneity (Table 1). When ethnicity was taken into account, a reduced risk of non-small cell lung carcinoma (NSCLC) was observed only among Asians (OR = 0.84, 95% CI = 0.79 to 0.90), and the cumulative evidence for association was strong (estimated PAR for risk allele rs401681[*C*] = 13%,major allele frequency = 60%).

Finally, no statistically significant relationship was observed for the other tumor types (breast, colon, endometrial cancer and TGCC) for which a meta-analysis could be performed; for breast and colon carcinomas, the cumulative evidence for lack of association was strong (Table 2).

rs402710. This *CLPTM1L* intronic SNP is in LD with many other *CLPTM1L* polymorphisms, including the above described rs401681 (see Supplementary Figure 2, available online), but not with *TERT* polymorphisms such as rs2736100, which led some authors to postulate that that the 5p15.33 locus might host two independent cancer risk SNPs (ie, rs2736100 and rs402710) (29). Ten studies reported a statistically significant association between the minor allele (*T*) and a decreased risk of lung, bladder and nasopharyngeal tumors, whereas two other studies described the opposite relationship with pancreatic and testicular cancer (Supplementary Table 1, available online).

Upon meta-analysis, rs402710[*T*] was associated with reduced risk of both bladder (OR = 0.85, 95% CI = 0.75 to 0.98) and lung cancer (OR = 0.87, 95% CI = 0.83 to 0.92), but in neither case was the cumulative evidence for association strong (Table 1).

Available data allowed a meta-analysis of lung cancer histological subtypes for risk assessment. Interestingly, rs402710[*T*] showed a homogeneous and statistically significantly reduced risk of both adenocarcinoma (OR = 0.84, 95% CI = 0.80 to 0.89) and SCC (OR = 0.83, 95% CI = 0.77 to 0.89), the cumulative evidence being strong in both cases (estimated PAR for risk allele rs402710[*C*] = 14%, risk allele frequency = 66%). Finally, no statistically significant association was found with the risk of pancreatic cancer (OR = 1.14, 95% CI = 0.98 to 1.32).

rs4635969. Considering the minor allele (*A*) of this *TERT*/*CLPTM1L* intergenic SNP, available studies reported opposing but statistically significant findings for lung cancer (decreased risk) and both pancreatic cancer and TGCC (increased risk). Meta-analysis by tumor type confirmed an association between rs4635969[*A*] and reduced risk of lung cancer (OR = 0.86, 95% CI = 0.82 to 0.90), although the cumulative evidence was weak because of a small overall association. As also reported for rs2736100, the reduced risk was more pronounced in lung adenocarcinoma (OR = 0.81, 95% CI = 0.75 to 0.88), for which the cumulative evidence for association could be classified as strong (estimated PAR for risk allele rs4635969[*G*] = 23%, major allele frequency = 80%).

Among rs4635969[*A*] carriers, the risk was statistically significantly increased for pancreatic (OR = 1.22, 95% CI = 1.14 to 1.32) and testicular (OR = 1.61, 95% CI = 1.46 to 1.76) carcinomas.. In these two cancers, the overall evidence for association was strong, the estimated PAR being 5% and 14%, respectively. Of note, the meta-risk for TGCC associated with this SNP was the strongest association found in the present meta-analysis.

rs465498. All four studies evaluating this intronic *CLPTM1L* SNP found a statistically significantly reduced cancer risk in people carrying the minor allele (*G*). Pooling the summary data confirmed this association (OR = 0.79, 95% CI = 0.74 to 0.84), although the cumulative evidence for association appeared moderate as a result of heterogeneity (I^2 = 49%, P = .12). Restricting the analysis to the Asian ancestry by pooling data from three series (a GWAS with one discovery and

two independent replication phases) resulted in a homogeneous (I^2 = 0%, P = .76) and statistically significant association with reduced risk of cancer (OR = 0.76, 95% CI = 0.72 to 0.81), which was statistically significantly lower ($P_{heterogeneity}$ = .021) than that reported in the study restricted to white subjects (OR = 0.85, 95% CI = 0.79 to 0.92) and the cumulative evidence was strong (estimated PAR for risk allele rs465498[*A*] among Asians = 36%, major allele frequency among Asians = 83%).

rs467095. The three studies reporting on the allele distribution of this intronic *CLPTM1L* polymorphism described a reduced cancer risk in people carrying the minor allele (*C*). Pooling the summary data confirmed the association of rs467095[*C*] with reduced cancer risk (OR = 0.83, 95% CI = 0.78 to 0.85), and the cumulative evidence for association was strong (estimated PAR for the risk allele rs467095[*T*] = 17%, major allele frequency ≈ 72%)

MNS16a. This variable tandem repeat polymorphism (short [*S*] vs long [*L*] polymorphism) is located downstream of the *TERT* gene and was reported to affect promoter activity in lung cancer cell lines (21), although the functional importance of the antisense transcript activity is unclear. Two studies on CNS tumors and one on breast cancer reported that the minor allele (*S*) was associated with an increased risk of disease development.

The meta-analysis showed that MNS16a[*S*] is associated with a homogeneously reported (I^2 = 8%, P = .30) statistically significantly increased risk of CNS tumors (OR = 1.20, 95% CI = 1.07 to 1.33; I^2 = 8%, P = .30), but not breast (OR = 1.20, 95% CI = 0.84 to 1.71) or lung (OR = 0.99, 95% CI = 0.62 to 1.60) carcinomas. The cumulative evidence for association between MNS16a[*S*] and CNS tumors was strong (estimated PAR = 7%, MAF = 34%).

Discussion

This work, to our knowledge, is the first synopsis of the literature on the role of polymorphisms at the *TERT* locus (5p15.33) in cancer predisposition. Upon systematic review and meta-analysis of the data from 85 molecular epidemiology studies, enrolling almost half a million people tested for one or more of 67 polymorphisms, which generated 494 allelic contrasts, we found that 22 polymorphisms were associated with the risk of developing one or more types of cancer, but only 11 showed strong cumulative evidence for association, according to the Venice criteria.

The risks were relatively low, with ORs for risk alleles ranging between 1.05 and 1.61 and those for protective alleles between 0.92 and 0.75. Accordingly, PAR, which takes into account both magnitude of the risk and risk allele frequency in the general population, varied from 4% to 36%. Although these figures might suggest at first glance that the *TERT* locus does not play a major role in cancer susceptibility, a couple of considerations should be made. First, it is widely recognized that single common polymorphisms are generally associated with low risks (ie, OR<1.5) (20), which calls for considering the effect of combinations of multiple polymorphisms. A few studies (29,37,54,63) addressed this issue by assessing the effect of *TERT* locus haplotypes on cancer risk: however, the haplotypes considered by different authors are heterogeneous and thus no meta-analysis could be performed. Other investigators have verified that some polymorphisms (eg, rs2736100 and rs2736098) carry a risk independently of others [eg, rs402710 (29), rs4635969 (40), and rs401681 (41)] using multivariable logistic regression analysis, but unfortunately the models (ie, the combination of included covariates) are not equal and thus their results cannot be merged. Nevertheless, to provide readers with an idea of the potential predictive value of multiple polymorphisms, we considered three unrelated (based on pairwise correlation coefficient r^2 <0.1 and multivariable analysis) polymorphisms (ie *TERT* rs2736100, intergenic rs4635969, and *CLPTM1L* rs402710) with a strong cumulative evidence for association with lung adenocarcinoma and we found that the estimated joint PAR defined by these polymorphisms is 41% (*see* Figure 1),

which corresponds to a 0.5% attributable community risk (considering a 1.2% lifetime risk of lung adenocarcinoma). Although we could calculate only a per-allele PAR (that is, only the co-dominant model was tested), this result highlights the pivotal role that *TERT* locus polymorphisms play in the determination of the most frequent histological subtype of lung cancer, and exemplifies the importance of further investigation on the 5p15.33 region with regard to cancer predisposition in general.

Another key point is that the *TERT* gene alone (without considering the rest of the *TERT* locus) has more than 500 known SNPs, whereas thus far the relationship with cancer risk has been investigated only for 67 SNPs, which is a minority of these polymorphisms. It should also be remembered that only 24 tumor types were investigated and that on average each polymorphism was tested for about three tumor types (range = 1-23)(*see* the heat-map in Supplementary Figure 3, available online). Furthermore, as we reported above, for many polymorphisms some evidence of association with cancer risk already exists, although more data are necessary to conclusively define their role (*see* Table 1 for polymorphisms with moderate or weak cumulative evidence; and Supplementary Table 1, available online for polymorphisms with statistically significant association in a single study). In contrast, only for a minority of the polymorphisms investigated to date (5 of 67 [7%]) the available results are compatible with no relevance for the susceptibility of three tumor types (*see* Table 2 for strong cumulative evidence), which does not rule out that these SNPs might be associated with the risk of other tumor types. Therefore, this synopsis, which strongly supports the relevance of the *TERT* locus to define the genetic architecture of cancer predisposition, also underscores that much work remains to be done before we can entirely appreciate the importance of this DNA region in cancer development.

The 5p15.33 locus is characterized by a 62 Kb linkage disequilibrium (LD) block including the 5'-end of *TERT*, its promoter and the entire gene *CLPTM1L* (Supplementary Figure 2, available online); consequently, there are two genes that can be involved in the tumor promoting effects

epidemiologically linked to the above described polymorphisms. Certainly *TERT* is the more appealing candidate because of its well-known role in telomere and tumor biology. However, we must underscore the discrepancy between the epidemiological findings associating *TERT* polymorphisms to cancer risk and the relatively scarce (29) and sometime conflicting evidence (59,87) associating the same polymorphisms to telomere length, a key aspect linking these chromosomal structures to cancer biology. In light of these controversies, more work is warranted to elucidate the molecular mechanisms possibly responsible for these epidemiological observations. For example, rs2736100 and other SNP in the locus are close to mutations known to alter telomerase activity (88). The complete sequencing of this locus in cancer patients will help investigators to fully elucidate the relationship between the *TERT* locus polymorphisms and cancer risk.

For the other gene in this region, *CLPTM1L* might be relevant not only because is in LD with *TERT* but also in the light of its own biological activity; its product (cleft lip and palate transmembrane protein 1-like protein) is known to induce cisplatin resistance in ovarian cancer cells (the CLPTM1L product is also called cisplatin resistance related protein [CRR9]) (89). Moreover, its SNP rs402710 has been recently associated with higher levels of bulky aromatic and hydrophobic DNA adducts (47), a typical product of lung cancer carcinogens such as polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines.

Considering that, for both genes, virtually all polymorphisms have no effect on protein sequence (all polymorphisms for which a meta-analysis could be performed were either intronic or exonic-synonymous or intergenic) (Supplementary Table 1, available online), the association of these polymorphisms with cancer susceptibility might derive from either their LD with still undetected functional polymorphisms (ie, exonic non-synonymous) or from their effect on protein expression (although the latter hypothesis does not appear to be supported by the evidence collected thus far, as mentioned above). Overall, the findings collected in this synopsis, which are virtually always based on tagging SNP, might tip the balance in favor of gene-centric strategies, that is, studies based on

the use of polymorphisms known to affect protein sequence. However, some investigators have recently reported no meaningful results adopting this approach, and have hypothesized that natural selection has rendered non-synonymous alleles so rare (ie, MAF<5%) that sample sizes greater than those utilized for common alleles should be used to detect statistically significant associations (90). Remembering that in this synopsis, where virtually all studies regarded polymorphisms with MAF greater than 5%, the mean sample size is approximately 6,000 subjects, the practical difficulty of carrying out gene-centric research is self-evident.

An intriguing finding of our work is that the association between a given polymorphism and cancer risk can be very specific not only in terms of ethnicity/histology but also in terms of effect direction (Table 1). Indeed we found that some 5p15.33 locus polymorphisms correlate (with strong evidence) with cancer risk only in whites (eg, rs2736100 in lung adenocarcinoma) or Asians (eg, rs402710 in lung cancer), and that others predispose to a specific histological subtype of cancer (eg, rs2736100 and rs4027100 in lung adenocarcinoma). More surprisingly, the same polymorphism (eg, rs2736100; rs401681) can result in an increased risk for some cancer types (eg, lung cancer; BCC) and a reduced risk for others (eg, TGCC; melanoma). In the case of melanoma and BCC, this finding, apparently contradictory, is in line with the opposite effect that telomere shortening (which is accelerated in rs401681[*C*] carriers (41)) can have on the two tumor types (91,92). On the other hand, our observation lends support to a double hypothesis: 1) no common molecular pathway leads to the development of all cancer types, and 2) some pathways favoring the development of some tumor types might even oppose the genesis of others. Some clinical epidemiology evidence is in the same direction: for example, women taking tamoxifen (a drug interfering with the estrogen receptor pathway) are at lower risk of breast but at higher risk of endometrial cancer; and people affected with skin melanoma (and thus with a genetic background predisposing to this tumor) are at higher risk of secondary melanoma but also at lower risk of gastrointestinal and lung tumors (93). Though

appealing, this hypothesis clearly warrants further investigation to be validated and thus to be exploitable on the clinical ground.

Finally, the limitations of this synopsis must be addressed. For example, although an exhaustive literature search was performed, it is possible that some publications were overlooked; moreover, not all the GWAS authors we contacted agreed to provide their data; finally, only for a minority of studies genotype data (either as raw or summary data) were provided, which enabled us to test only the co-dominant model (per-allele risk analysis). We hope that this large collection of data on *TERT* locus polymorphisms and cancer risk will prompt investigators to share their knowledge in this field, also exploiting the dedicated online data repository above mentioned (available at http://www.mmmp.org) (13). Furthermore, we used allele counts and crude estimates of effect, rather than association estimates adjusted by other polymorphisms, genes or even environmental factors. As discussed above, for interaction between polymorphisms, the models used in single eligible studies differ in most cases and were therefore unsuitable for pooling. Lung cancer was the only tumor type for which investigators often reported data adjustment for smoking, the most common environmental risk factor. In this case, the impact of *TERT* locus polymorphisms was generally unaffected by smoking (80), which strengthens the findings of our meta-analysis, although it does not rule out other confounding factors [eg, chronic obstructive pulmonary disease (84)]. Again, even for lung cancer the adjustment for smoking was reported in different ways (eg, as a single OR adjusted by including smoking behavior in a logistic regression model or by providing multiple OR obtained separately in smoking and non-smoking subjects), which precluded any meaningful pooling of summary data.

For gene-gene interactions, it should be remembered that tens of genes are currently known to contribute to telomere biology (94) and thus may contribute to modulate cancer susceptibility. However, to date only a few authors investigated the relationship between polymorphisms of telomere-related genes (other than *TERT*) and predisposition to few tumor types

(24,28,37,45,60,62,75), and because the available results are sparse (different tumor types), no data merging could be performed, which calls for further research in this field.

Multiple testing is another possible concern. We performed a total of 118 meta-analyses (including ethnicity-specific and cancer subtype-specific analyses): considering a Bonferroni adjustment, the *P* value threshold for statistical significance would be .0004, which would reduce statistically significant associations from 75 to 47 (Table 1, *P* values tagged with symbols). Nevertheless, it should be noted that this *P* value is overly conservative because many tests were performed in independent data sets. Furthermore, lowering the alpha level of significance increases the possibility of type II error (ie, reduces statistical power). More importantly, polymorphisms statistically significantly associated with cancer risk were graded according to the Venice criteria, providing evidence over and above statistical *P* values.

In conclusion, this synopsis demonstrates that genetic variation in the *TERT* locus is likely to play a relevant role in cancer development. However, it also underscores that much work still needs to be done to clarify the molecular mechanisms underlying this epidemiological observation and to define the interactions of this evidence with the other pieces of the cancer predisposition puzzle.

Figure legend

Figure 1. Flow chart for the estimation of the joint risk of lung adenocarcinoma in the general population attributable to three *TERT* locus polymorphisms. Top panel. A forest plot depicting the meta-analysis of the studies that contributed to define the association between the minor alleles of three single nucleotide polymorphisms (SNPs) and the risk of developing lung adenocarcinoma. Open squares represent odds ratios (OR) of single studies (the width of each square is proportional to the weight of the corresponding study; the horizontal line represents the 95% confidence interval [CI] of the study OR); solid black diamonds represent summary OR for each SNP (the width of each diamond is proportional to the 95% CI of the corresponding summary OR). Bottom left panel.Only SNP showing strong cumulative evidence for association with lung adenocarcinoma were selected. Cumulative evidence was assessed as per the Venice criteria (see text for more details). OR refer to risk alleles (alleles associated with increased cancer risk). Bottom right panel. The joint PAR (population attributable risk) represents the proportion of lung adenocarcinoma cases estimated to be attributable to the three SNP showing strong cumulative evidence of association; it depends on both the magnitude of the association (OR) and the risk allele frequency in the general population.

Table 1. TERT locus polymorphisms for which the meta-analysis demonstrated a statistically significant association with cancer risk *

POLYMORPHISM DATA			STUDY FEATURES					META-ANALYSIS FINDINGS				
Polymorphism ID	**Gene**	**Allele**	**Race or ethnicity**	**No. of studies**	**Case subjects, No.**	**Control subjects, No.**	**Cancer**	**OR (95% CI)**	***P* for Z-test** †	**I^2 (%)**	***P* for Q test** †	**Level of evidence** ‡
rs13167280	*TERT*	*T*	White	2	1581	1889	Bladder	1.23 (1.07 to 1.42)	.004	0	.45	BAA/moderate
rs1801075	Intergenic	*C*	Miscellany §	4	3552	4340	Lung (miscellany ‖)	0.88 (0.80 to 0.96)	.006	0	.49	AAC/weak
rs2242652	*TERT*	*T*	White	4	33600	32419	Prostate	0.82 (0.76 to 0.89)	9.0E-07¶	61	.05	ACA/weak
rs2735845	Intergenic	*G*	Miscellany	3	7213	7523	Lung (miscellany)	1.11 (1.05 to 1.17)	2.3E-04¶	0	.39	AAC/weak
rs2736098	*TERT*	*A*	Miscellany	3	4617	10134	Bladder	1.19 (1.12 to 1.25)	8.6E-10¶	0	.87	AAA/strong
rs2736098	*TERT*	*A*	Miscellany	4	6949	12492	Lung (miscellany)	1.21 (1.15 to 1.27)	2.2E-13¶	0	.99	AAA/strong
rs2736100	*TERT*	*C*	Miscellany	2	970	1072	Bladder	1.19 (1.05 to 1.34)	.007	0	.64	BAA/moderate
rs2736100	*TERT*	*C*	Miscellany	6	6871	12449	CNS	1.34 (1.23 to 1.46)	4.4E-11¶	60	.029	ACA/weak
rs2736100	*TERT*	*C*	White	5	5918	11413	CNS	1.35 (1.22 to 1.50)	1.2E-08¶	65	.021	ACA/weak
rs2736100	*TERT*	*C*	Miscellany	23	50917	72598	Lung (miscellany)	1.19 (1.14 to 1.23)	<1.0E-16¶	77	2.9E-11	ACA/weak
rs2736100	*TERT*	*C*	White	11	30650	41248	Lung (miscellany)	1.11 (1.08 to 1.15)	1.1E-12¶	35	.12	AAC/weak
rs2736100	*TERT*	*C*	Asian	12	20267	31350	Lung (miscellany)	1.26 (1.20 to 1.32)	<1.0E-16¶	68	3.5E-04	ACB/weak
rs2736100	*TERT*	*C*	Miscellany	14	22045	68197	Lung (adenocarcinoma)	1.30 (1.25 to 1.36)	<1.0E-16¶	62	.001	ACB/weak
rs2736100	*TERT*	*C*	Miscellany	13	11645	57483	Lung (squamous)	1.06 (1.01 to 1.12)	.017	54	.011	ACC/weak
rs2736100	*TERT*	*C*	Miscellany	29	35509	61787	Lung (NSCLC)	1.19 (1.14 to 1.25)	3.3E-14¶	80	1.1E-16	ACA/weak
rs2736100	*TERT*	*C*	White	6	9540	37840	Lung (adenocarcinoma)	1.22 (1.17 to 1.27)	<1.0E-16¶	0	.42	AAA/strong
rs2736100	*TERT*	*C*	Asian	8	12505	30357	Lung (adenocarcinoma)	1.35 (1.29 to 1.42)	<1.0E-16¶	47	.06	ABA/moderate
rs2736100	*TERT*	*C*	White	6	6626	37840	Lung (squamous)	1.05 (1.00 to 1.10)	.043	30	.21	ABA/moderate
rs2736100	*TERT*	*C*	White	13	16572	37840	Lung (NSCLC)	1.15 (1.09 to 1.22)	1.2E-06¶	73	9.2E-06	ACA/weak
rs2736100	*TERT*	*C*	Asian	16	18937	23947	Lung (NSCLC)	1.24 (1.16 to 1.31)	2.4E-12¶	74	5.2E-07	ACA/weak
rs2736100	*TERT*	*C*	White	2	3851	3934	Pancreas	1.12 (1.04 to 1.20)	.001	0	.77	AAC/weak
rs2736100	*TERT*	*C*	White	3	1959	8679	Testis	0.75 (0.70 to 0.81)	4.4E-16¶	0	.62	AAA/strong
rs2853668	Intergenic	*T*	White	2	11067	12517	Colon	0.90 (0.82 to 0.99)	.034	72	.05	ACC/weak
rs2853668	Intergenic	*T*	Miscellany	2	5531	6284	Lung (miscellany)	1.09 (1.02 to 1.15)	.009	0	.66	AAC/weak
rs2853668	Intergenic	*T*	White	2	3851	3934	Pancreas	0.92 (0.85 to 0.99)	.046	0	.68	AAC/weak
rs2853676	*TERT*	*A*	Miscellany	4	6010	8313	CNS	1.26 (1.21 to 1.32)	<1.0E-16¶	0	.58	AAA/strong
rs2853676	*TERT*	*A*	Miscellany	3	11205	11957	Lung (miscellany)	1.06 (1.01 to 1.10)	.008	0	.79	AAC/weak
rs31489	*CLPTM1L*	*A*	Miscellany	6	13929	16047	Lung (miscellany)	0.83 (0.78 to 0.88)	4.2E-09¶	55	.05	ACA/weak
rs31489	*CLPTM1L*	*A*	White	4	10594	11070	Lung (miscellany)	0.84 (0.78 to 0.90)	1.5E-06¶	58	.07	ACA/weak
rs31489	*CLPTM1L*	*A*	Asian	2	3335	4977	Lung (miscellany)	0.80 (0.70 to 0.91)	.001	44	.18	ABA/moderate
rs31489	*CLPTM1L*	*A*	White	2	3851	3934	Pancreas	1.18 (1.06 to 1.32)	.003	70	.06	ACA/weak
rs31489	*CLPTM1L*	*A*	White	2	1191	5805	Testis	1.28 (1.16 to 1.41)	1.4E-06¶	18	.27	AAA/strong
rs380286	*CLPTM1L*	*A*	Miscellany	2	5529	6289	Lung (miscellany)	0.85 (0.80 to 0.91)	5.8E-07¶	0	.84	AAA/strong
rs401681	*CLPTM1L*	*T*	Miscellany	4	8645	41188	Bladder	0.89 (0.86 to 0.92)	9.2E-11¶	0	.81	AAC/weak
rs401681	*CLPTM1L*	*T*	White	3	4152	32824	Pancreas	1.14 (1.01 to 1.29)	.037	77	.013	ACC/weak
rs401681	*CLPTM1L*	*T*	White	3	11235	74276	Prostate	0.92 (0.89 to 0.95)	3.8E-06¶	0	.63	AAC/weak
rs401681	*CLPTM1L*	*T*	White	3	3941	32808	BCC (skin)	0.82 (0.76 to 0.89)	4.2E-06¶	49	.14	ABA/moderate
rs401681	*CLPTM1L*	*T*	White	5	8012	38925	Melanoma (skin)	1.12 (1.03 to 1.22)	.006	72	.007	ACC/weak
rs401681	*CLPTM1L*	*T*	White	3	1478	30525	SCC (skin)	0.92 (0.84 to 0.99)	.046	0	.57	AAC/weak
rs401681	*CLPTM1L*	*T*	Miscellany	12	25674	58027	Lung (miscellany)	0.87 (0.84 to 0.90)	<1.0E-16¶	33	.13	ABA/moderate
rs401681	*CLPTM1L*	*T*	White	8	18641	48866	Lung (miscellany)	0.87 (0.84 to 0.90)	3.5E-14¶	34	.15	ABA/moderate
rs401681	*CLPTM1L*	*T*	Asian	4	7033	9161	Lung (miscellany)	0.86 (0.81 to 0.93)	2.9E-05¶	46	.13	ABA/moderate
rs401681	*CLPTM1L*	*T*	Miscellany	6	5900	43343	Lung (adenocarcinoma)	0.87 (0.81 to 0.93)	4.3E-05¶	52	.06	ACA/weak

rs401681	*CLPTM1L*	*T*	Miscellany	5	5319	40522	Lung (squamous)	0.85 (0.76 to 0.96)	.010	72	.006	ACA/weak
rs401681	*CLPTM1L*	*T*	Miscellany	12	11852	53575	Lung (NSCLC)	0.86 (0.82 to 0.91)	1.9E-07¶	56	.01	ACA/weak
rs401681	*CLPTM1L*	*T*	White	3	2231	37259	Lung (adenocarcinoma)	0.90 (0.82 to 0.98)	.019	45	.16	ABC/weak
rs401681	*CLPTM1L*	*T*	Asian	3	3669	6084	Lung (adenocarcinoma)	0.84 (0.76 to 0.93)	7.5E-04	57	.10	ACA/weak
rs401681	*CLPTM1L*	*T*	Asian	2	736	4184	Lung (squamous)	0.85 (0.75 to 0.96)	.010	0	.95	BAA/moderate
rs401681	*CLPTM1L*	*T*	White	7	7447	43307	Lung (NSCLC)	0.87 (0.80 to 0.95)	.001	67	.01	ACA/weak
rs401681	*CLPTM1L*	*T*	Asian	5	4405	10268	Lung (NSCLC)	0.84 (0.79 to 0.90)	1.5E-07¶	14	.32	AAA/strong
rs402710	*CLPTM1L*	*T*	Miscellany	2	974	1055	Bladder	0.85 (0.75 to 0.98)	.022	0	.36	BAA/moderate
rs402710	*CLPTM1L*	*T*	Miscellany	12	31364	35462	Lung (miscellany)	0.88 (0.83 to 0.92)	8.1E-07¶	65	.002	ACC/weak
rs402710	*CLPTM1L*	*T*	White	8	24471	26161	Lung (miscellany)	0.89 (0.84 to 0.94)	5.2E-05¶	69	.004	ACC/weak
rs402710	*CLPTM1L*	*T*	Asian	4	6893	9301	Lung (miscellany)	0.87 (0.82 to 0.91)	8.2E-08¶	9	.35	AAA/strong
rs402710	*CLPTM1L*	*T*	Miscellany	3	4929	15011	Lung (adenocarcinoma)	0.84 (0.80 to 0.89)	5.9E-10¶	0	.42	AAA/strong
rs402710	*CLPTM1L*	*T*	Miscellany	3	2461	15011	Lung (squamous)	0.83 (0.77 to 0.89)	4.1E-07¶	0	.94	AAA/strong
rs402710	*CLPTM1L*	*T*	Miscellany	8	8945	31783	Lung (NSCLC)	0.84 (0.81 to 0.88)	2.2E-16¶	0	.78	AAA/strong
rs4246742	*TERT*	*T*	Miscellany	2	5528	6274	Lung (miscellany)	1.08 (1.01 to 1.15)	.018	0	.83	AAC/weak
rs451360	*CLPTM1L*	*A*	Miscellany	3	6983	8058	Lung (miscellany)	0.80 (0.70 to 0.92)	.001	70	.035	ACB/weak
rs451360	*CLPTM1L*	*A*	White	2	4652	4981	Lung (miscellany)	0.85 (0.76 to 0.95)	.004	48	.16	ABA/moderate
rs452384	*CLPTM1L*	*C*	Miscellany	2	5302	6823	Lung (miscellany)	0.82 (0.74 to 0.90)	7.4E-05¶	52	.15	ACA/weak
rs452932	*CLPTM1L*	*C*	Miscellany	2	5302	6823	Lung (miscellany)	0.82 (0.74 to 0.90)	7.4E-05¶	52	.15	ACA/weak
rs4635969	Intergenic	*A*	Miscellany	4	12893	13126	Lung (miscellany)	0.86 (0.82 to 0.90)	8.1E-10¶	8	.35	AAA/strong
rs4635969	Intergenic	*A*	Miscellany	2	3674	8230	Lung (adenocarcinoma)	0.81 (0.75 to 0.88)	1.2E-06¶	0	.87	AAA/strong
rs4635969	Intergenic	*A*	Miscellany	2	1594	8230	Lung (squamous)	0.87 (0.78 to 0.97)	.010	0	.45	AAA/strong
rs4635969	Intergenic	*A*	Miscellany	4	5268	8230	Lung (NSCLC)	0.83 (0.78 to 0.89)	6.0E-08¶	0	.69	AAA/strong
rs4635969	Intergenic	*A*	White	2	3851	3934	Pancreas	1.22 (1.14 to 1.32)	1.1E-07¶	0	.86	AAA/strong
rs4635969	Intergenic	*A*	White	3	1729	9079	Testis	1.61 (1.47 to 1.75)	<1.0E-16¶	0	.77	AAA/strong
rs465498	*CLPTM1L*	*G*	Miscellany	4	11579	13190	Lung (miscellany)	0.79 (0.74 to 0.84)	2.6E-12¶	49	.12	ABA/moderate
rs465498	*CLPTM1L*	*G*	Asian	3	8608	9444	Lung (miscellany)	0.76 (0.72 to 0.81)	<1.0E-16¶	0	.76	AAA/strong
rs467095	*CLPTM1L*	*C*	Miscellany	3	7739	9271	Lung (miscellany)	0.83 (0.78 to 0.87)	3.9E-11¶	0	.37	AAA/strong
rs4975615	Intergenic	*G*	Miscellany	3	6983	8058	Lung (miscellany)	0.81 (0.76 to 0.87)	2.7E-10¶	26	.26	ABA/moderate
rs4975616	Intergenic	*G*	Miscellany	7	12743	14130	Lung (miscellany)	0.83 (0.79 to 0.88)	1.1E-11¶	41	.12	ABA/moderate
rs4975616	Intergenic	*G*	White	2	3851	3934	Pancreas	0.85 (0.78 to 0.94)	.001	57	.13	ACA/weak
rs4975616	Intergenic	*G*	White	2	1328	5861	Testis	1.20 (1.03 to 1.40)	.016	55	.13	ACA/weak
MNS16a	*TERT*	*S*	White	2	1764	1664	CNS	1.19 (1.07 to 1.33)	.001	8	.30	AAA/strong

* Telomerase reverse transcriptase (*TERT*) locus includes *TERT* and cleft lip and palate transmembrane 1-like (*CLPTM1L*) genes. OR = odds ratio; CI = confidence interval; BCC = basal cell carcinoma; SCC =squamous cell carcinoma; CNS =central nervous system; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

† All *P* values calculated by Z-test or Q test were two-sided.

‡ A,B, and C represent the Venice criteria grades for amount of evidence, replication of association and protection from bias, which ultimately define the level of cumulative evidence (strong, moderate, weak).

§ Mix of different races.

‖ Mix of different histological subtypes.

¶ Statistically significant *P* values after Bonferroni adjustment for multiple testing.

Table 2. *TERT* locus polymorphisms for which the meta-analysis demonstrated no nominally statistically significant association with cancer risk *

POLYMORPHISM DATA			STUDY CHARACTERISTIC					META-ANALYSIS FINDINGS				
Polymorphism ID	**Gene**	**Allele**	**Race or ethnicity**	**No. of studies**	**Case Subjects, No.**	**Control subjects, No.**	**Cancer type**	**OR (95% CI)**	***P* for Z-test** †	I^2, %	***P* for Q test** †	**Level of evidence** ‡
rs10073340	*CLPTM1L*	*T*	White	2	3851	3934	Pancreas	0.95 (0.73 to 1.23)	.68	89	.002	weak
rs13167280	*TERT*	*T*	White	2	2989	3360	Breast	1.02 (0.91 to 1.16)	.69	0	.82	weak
rs2075786	*TERT*	*T*	White	2	2953	3333	Breast	1.01 (0.94 to 1.09)	.77	0	.45	weak
rs2075786	*TERT*	*T*	Miscellany §	4	3134	3130	Lung (miscellany ‖)	1.31 (0.98 to 1.75)	.06	74	.01	weak
rs2075786	*TERT*	*T*	Asian/Black	3	2770	2750	Lung (miscellany)	1.45 (0.88 to 2.37)	.14	82	.004	weak
rs2242652	*TERT*	*T*	Miscellany	2	4619	5360	Lung (miscellany)	1.06 (0.94 to 1.19)	.36	48	.17	weak
rs2735940	Intergenic	*T*	White	2	1453	2584	Bladder	0.96 (0.87 to 1.05)	.37	0	.77	weak
rs2735940	Intergenic	*T*	White	2	3180	3405	Breast	0.99 (0.93 to 1.07)	.92	0	.99	weak
rs2735940	Intergenic	*T*	Miscellany	6	3682	4099	Lung (miscellany)	1.08 (0.95 to 1.23)	.25	59	.032	weak
rs2735940	Intergenic	*T*	White	3	2746	3166	Lung (miscellany)	1.04 (0.89 to 1.22)	.62	65	.06	weak
rs2735940	Intergenic	*T*	Asian/Black	3	936	933	Lung (miscellany)	1.20 (0.84 to 1.72)	.32	64	.06	weak
rs2736098	*TERT*	*A*	Miscellany	2	1102	1182	CNS	1.07 (0.77 to 1.48)	.69	56	.13	weak
rs2736098	*TERT*	*A*	White	2	8708	48804	Prostate	1.10 (1.00 to 1.20)	.05	83	.015	weak
rs2736100	*TERT*	*C*	Miscellany	9	6002	50492	Lung (SCLC)	1.05 (0.99 to 1.10)	.06	13	.33	strong
rs2736100	*TERT*	*C*	Asian	7	5019	19643	Lung (squamous)	1.08 (0.98 to 1.18)	.11	53	.05	weak
rs2736100	*TERT*	*C*	White	2	3341	4533	Melanoma (skin)	1.03 (0.95 to 1.11)	.46	0	.62	weak
rs2736109	Intergenic	*A*	White	2	2967	3331	Breast	0.96 (0.75 to 1.23)	.76	90	.001	weak
rs2736122	*TERT*	*T*	Miscellany	3	11215	11908	Lung (miscellany)	0.97 (0.92 to 1.01)	.19	0	.80	strong
rs2736122	*TERT*	*T*	Miscellany	2	3851	3934	Pancreas	1.00 (0.93 to 1.08)	.94	0	.37	weak
rs2853669	Intergenic	*C*	White	3	3787	3824	Breast	1.02 (0.91 to 1.14)	.76	52	.12	weak
rs2853676	*TERT*	*A*	Miscellany	2	3851	3934	Pancreas	0.93 (0.86 to 1.00)	.06	0	.40	weak
rs2853676	*TERT*	*A*	White	2	3349	4542	Melanoma (skin)	1.16 (0.81 to 1.66)	.42	88	.003	weak
rs2853677	*TERT*	*C*	White	2	2963	3340	Breast	1.03 (0.96 to 1.10)	.43	0	.53	weak
rs2853677	*TERT*	*C*	Miscellany	4	2252	1809	Lung (miscellany)	1.31 (0.97 to 1.75)	.073	63	.046	weak
rs2853677	*TERT*	*C*	White	2	2045	1615	Lung (miscellany)	1.34 (0.88 to 2.06)	.17	76	.04	weak
rs2853677	*TERT*	*C*	Asian/Black	2	207	194	Lung (miscellany)	1.38 (0.62 to 3.05)	.43	74	.05	weak
rs2853690	*TERT*	*T*	White	2	2983	3340	Breast	0.98 (0.89 to 1.08)	.74	0	.60	weak
rs2853690	*TERT*	*T*	Miscellany	2	459	483	Lung (NSCLC)	0.89 (0.63 to 1.25)	.51	0	.75	weak
rs31484	*CLPTM1L*	*T*	Miscellany	2	5302	6823	Lung (miscellany)	0.95 (0.61 to 1.48)	.83	97	2.1E-10	weak
rs401681	*CLPTM1L*	*T*	White	3	10254	36832	Breast	1.01 (0.97 to 1.05)	.65	0	.47	strong
rs401681	*CLPTM1L*	*T*	White	4	5124	33326	Colon	1.05 (0.98 to 1.12)	.15	36	.20	strong
rs401681	*CLPTM1L*	*T*	White	2	1095	30463	Endometrium	0.94 (0.73 to 1.21)	.61	86	.007	weak
rs401681	*CLPTM1L*	*T*	White	2	1328	5861	Testis	1.18 (0.99 to 1.40)	.06	67	.08	weak
rs401681	*CLPTM1L*	*T*	Miscellany	3	1573	37295	Lung (SCLC)	0.98 (0.90 to 1.07)	.66	9	.33	weak
rs401681	*CLPTM1L*	*T*	White	3	4583	36338	Lung (squamous)	0.85 (0.70 to 1.04)	.11	86	.001	weak
rs402710	*CLPTM1L*	*T*	White	2	3851	3934	Pancreas	1.14 (0.98 to 1.33)	.10	83	.014	weak
rs466502	*CLPTM1L*	*G*	Miscellany	2	5302	6823	Lung (miscellany)	0.96 (0.65 to 1.42)	.84	97	8.2E-09	weak
rs4975605	*TERT*	*A*	Miscellany	3	11177	11835	Lung (miscellany)	0.96 (0.92 to 1.00)	.06	0	.94	strong
rs4975605	*TERT*	*A*	White	2	3851	3934	Pancreas	1.03 (0.96 to 1.10)	.39	0	.64	weak
rs7712562	Intergenic	*C*	White	2	2965	3341	Breast	1.00 (0.82 to 1.21)	.97	70	.06	weak
rs7727912	*CLPTM1L*	*T*	White	2	4652	4981	Lung (miscellany)	1.01 (0.74 to 1.39)	.94	85	.01	weak
MNS16a	*TERT*	*S*	Miscellany	2	2058	2194	Breast	1.20 (0.84 to 1.71)	.32	85	.01	weak

MNS16a	*TERT*	*S*	Miscellany	2	990	1015	Lung (NSCLC)	0.99 (0.62 to 1.60)	.98	61	.11	weak

* Telomerase reverse transcriptase (*TERT*) locus includes *TERT* and cleft lip and palate transmembrane 1-like (*CLPTM1L*) genes. OR: odds ratio; CI: confidence interval; CNS: central nervous system; NSCLC: non small cell lung cancer; SCLC: small cell lung cancer.
† All *P* values calculated by Z-test or Q test were two-sided.
‡ Levels of cumulative evidence (strong *vs* weak) were defined according to statistical power and between-study heterogeneity.
§ Mix of different races.
‖ Mix of different histological subtypes.

References

1. Blackburn EH. Switching and signaling at the telomere. Cell 2001;106:661-73.
2. de Lange T. How telomeres solve the end-protection problem. Science 2009;326:948-52.
3. Bianchi A, Shore D. How telomerase reaches its end: mechanism of telomerase regulation by the telomeric complex. Mol Cell 2008;31:153-65.
4. Osterhage JL, Friedman KL. Chromosome end maintenance by telomerase. J Biol Chem 2009;284:16061-5.
5. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet 2005;6:611-22.
6. Calado RT, Young NS. Telomere diseases. N Engl J Med 2009;361:2353-65.
7. Harley CB. Telomerase and cancer therapeutics. Nat Rev Cancer 2008;8:167-79.
8. Liu JP, Chen W, Schwarer AP, Li H. Telomerase in cancer immunotherapy. Biochim Biophys Acta 2010;1805:35-42.
9. Baird DM. Variation at the TERT locus and predisposition for cancer. Expert Rev Mol Med 2010;12:e16.
10. Ioannidis JP, Boffetta P, Little J, O'Brien TR, Uitterlinden AG, Vineis P, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol 2008;37:120-32.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
13. Mocellin S, Rossi CR. The Melanoma Molecular Map Project. Melanoma Res 2008;18:163-5.

14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

15. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53:1119-29.

16. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.

17. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. Clin Trials 2007;4:245-53.

18. Stacey SN, Sulem P, Masson G, Gudjonsson SA, Thorleifsson G, Jakobsdottir M, et al. New common variants affecting susceptibility to basal cell carcinoma. Nat Genet 2009;41:909-14.

19. Watcholder S. The impact of a prevention effort on the community. Epidemiology 2005;16:1-3.

20. Sagoo GS, Little J, Higgins JP. Systematic reviews of genetic association studies. Human Genome Epidemiology Network. PLoS Med 2009;6:e28.

21. Wang L, Soria JC, Chang YS, Lee HY, Wei Q, Mao L. Association of a functional tandem repeats in the downstream of human telomerase gene and lung cancer. Oncogene 2003;22:7123-9.

22. Carpentier C, Lejeune J, Gros F, Everhard S, Marie Y, Kaloshi G, et al. Association of telomerase gene hTERT polymorphism and malignant gliomas. J Neurooncol 2007;84:249-53.

23. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, Hankinson SE, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007;39:870-4.

24. Savage SA, Chanock SJ, Lissowska J, Brinton LA, Richesson D, Peplonska B, et al. Genetic variation in five genes important in telomere biology and risk for breast cancer. Br J Cancer 2007;97:832-6.

25. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39:645-9.

26. Amos CI, Wu X, Broderick P, Gorlov IP, Gu J, Eisen T, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 2008;40:616-22.

27. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, et al. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40:316-21.

28. Hosgood HD, 3rd, Menashe I, Shen M, Yeager M, Yuenger J, Rajaraman P, et al. Pathway-based evaluation of 380 candidate genes and lung cancer susceptibility suggests the importance of the cell cycle pathway. Carcinogenesis 2008;29:1938-43.

29. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet 2008;40:1404-6.

30. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 2008;452:638-42.

31. Tomlinson IP, Webb E, Carvajal-Carmona L, Broderick P, Howarth K, Pittman AM, et al. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. Nat Genet 2008;40:623-30.

32. Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet 2008;40:1407-9.

33. Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. Nat Genet 2009;41:986-90.

34. Andersson U, Osterman P, Sjostrom S, Johansen C, Henriksson R, Brannstrom T, et al. MNS16A minisatellite genotypes in relation to risk of glioma and meningioma and to glioblastoma outcome. Int J Cancer 2009;125:968-72.

35. Andrew AS, Gui J, Sanderson AC, Mason RA, Morlock EV, Schned AR, et al. Bladder cancer SNP panel predicts susceptibility and survival. Hum Genet 2009;125:527-39.

36. Calado RT, Regal JA, Hills M, Yewdell WT, Dalmazzo LF, Zago MA, et al. Constitutional hypomorphic telomerase mutations in patients with acute myeloid leukemia. Proc Natl Acad Sci U S A 2009;106:1187-92.

37. Choi JE, Kang HG, Jang JS, Choi YY, Kim MJ, Kim JS, et al. Polymorphisms in telomere maintenance genes and risk of lung cancer. Cancer Epidemiol Biomarkers Prev 2009;18:2773-81.

38. Falchi M, Bataille V, Hayward NK, Duffy DL, Bishop JA, Pastinen T, et al. Genome-wide association study identifies variants at 9p21 and 22q13 associated with development of cutaneous nevi. Nat Genet 2009;41:915-9.

39. Jin G, Xu L, Shu Y, Tian T, Liang J, Xu Y, et al. Common genetic variants on 5p15.33 contribute to risk of lung adenocarcinoma in a Chinese population. Carcinogenesis 2009;30:987-90.

40. Landi MT, Chatterjee N, Yu K, Goldin LR, Goldstein AM, Rotunno M, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet 2009;85:679-91.

41. Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet 2009;41:221-7.

42. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet 2009;41:899-904.

43. Song W, Ruder AM, Hu L, Li Y, Ni R, Shao W, et al. Genetic epidemiology of glioblastoma multiforme: confirmatory and new findings from analyses of human leukocyte antigen alleles and motifs. PLoS One 2009;4:e7157.

44. Van Dyke AL, Cote ML, Wenzlaff AS, Abrams J, Land S, Iyer P, et al. Chromosome 5p Region SNPs Are Associated with Risk of NSCLC among Women. J Cancer Epidemiol 2009;2009:242151.

45. Varadi V, Brendle A, Grzybowska E, Johansson R, Enquist K, Butkiewicz D, et al. A functional promoter polymorphism in the TERT gene does not affect inherited susceptibility to breast cancer. Cancer Genet Cytogenet 2009;190:71-4.

46. Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nat Genet 2009;41:905-8.

47. Zienolddiny S, Skaug V, Landvik NE, Ryberg D, Phillips DH, Houlston R, et al. The TERT-CLPTM1L lung cancer susceptibility variant associates with higher DNA adduct formation in the lung. Carcinogenesis 2009;30:1368-71.

48. Bei JX, Li Y, Jia WH, Feng BJ, Zhou G, Chen LZ, et al. A genome-wide association study of nasopharyngeal carcinoma identifies three new susceptibility loci. Nat Genet 2010;42:599-603.

49. Clifford RJ, Zhang J, Meerzaman DM, Lyu MS, Hu Y, Cultraro CM, et al. Genetic variations at loci involved in the immune response are risk factors for hepatocellular carcinoma. Hepatology 2010;52:2034-43.

50. Gudmundsson J, Besenbacher S, Sulem P, Gudbjartsson DF, Olafsson I, Arinbjarnarson S, et al. Genetic correction of PSA values using sequence variants associated with PSA levels. Sci Transl Med 2010;2:62ra92.

51. Guey LT, Garcia-Closas M, Murta-Nascimento C, Lloreta J, Palencia L, Kogevinas M, et al. Genetic susceptibility to distinct bladder cancer subphenotypes. Eur Urol 2010;57:283-92.

52. Hsiung CA, Lan Q, Hong YC, Chen CJ, Hosgood HD, Chang IS, et al. The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. PLoS Genet 2010;6.

53. Johnatty SE, Beesley J, Chen X, Macgregor S, Duffy DL, Spurdle AB, et al. Evaluation of candidate stromal epithelial cross-talk genes identifies association between risk of serous ovarian cancer and TERT, a cancer susceptibility "hot-spot". PLoS Genet 2010;6:e1001016.

54. Kohno T, Kunitoh H, Shimada Y, Shiraishi K, Ishii Y, Goto K, et al. Individuals susceptible to lung adenocarcinoma defined by combined HLA-DQA1 and TERT genotypes. Carcinogenesis 2010;31:834-41.

55. Lascorz J, Forsti A, Chen B, Buch S, Steinke V, Rahner N, et al. Genome-wide association study for colorectal cancer identifies risk polymorphisms in German familial cases and implicates MAPK signalling pathways in disease susceptibility. Carcinogenesis 2010;31:1612-9.

56. Liu Z, Li G, Wei S, Niu J, Wang LE, Sturgis EM, et al. Genetic variations in TERT-CLPTM1L genes and risk of squamous cell carcinoma of the head and neck. Carcinogenesis 2010;31:1977-81.

57. Miki D, Kubo M, Takahashi A, Yoon KA, Kim J, Lee GK, et al. Variation in TP63 is associated with lung adenocarcinoma susceptibility in Japanese and Korean populations. Nat Genet 2010;42:893-6.

58. Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet 2010;42:224-8.

59. Pooley KA, Tyrer J, Shah M, Driver KE, Leyland J, Brown J, et al. No association between TERT-CLPTM1L single nucleotide polymorphism rs401681 and mean telomere length or cancer risk. Cancer Epidemiol Biomarkers Prev 2010;19:1862-5.

60. Prescott J, McGrath M, Lee IM, Buring JE, De Vivo I. Telomere length and genetic analyses in population-based studies of endometrial cancer risk. Cancer 2010;116:4275-82.

61. Rothman N, Garcia-Closas M, Chatterjee N, Malats N, Wu X, Figueroa JD, et al. A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. Nat Genet 2010;42:978-84.

62. Shen J, Gammon MD, Wu HC, Terry MB, Wang Q, Bradshaw PT, et al. Multiple genetic variants in telomere pathway genes and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2010;19:219-28.

63. Truong T, Hung RJ, Amos CI, Wu X, Bickeboller H, Rosenberger A, et al. Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. J Natl Cancer Inst 2010;102:959-71.

64. Turnbull C, Rapley EA, Seal S, Pernet D, Renwick A, Hughes D, et al. Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. Nat Genet 2010;42:604-7.

65. Wang Y, Broderick P, Matakidou A, Eisen T, Houlston RS. Role of 5p15.33 (TERT-CLPTM1L), 6p21.33 and 15q25.1 (CHRNA5-CHRNA3) variation and lung cancer risk in never-smokers. Carcinogenesis 2010;31:234-8.

66. Yang P, Li Y, Jiang R, Cunningham JM, Zhang F, de Andrade M. A rigorous and comprehensive validation: common genetic variations and lung cancer. Cancer Epidemiol Biomarkers Prev 2010;19:240-4.

67. Yoon KA, Park JH, Han J, Park S, Lee GK, Han JY, et al. A genome-wide association study reveals susceptibility variants for non-small cell lung cancer in the Korean population. Hum Mol Genet 2010;19:4948-54.

68. Yoon SL, Jung SI, Do EJ, Lee SR, Lee SY, Chu IS, et al. Short rare hTERT-VNTR2-2nd alleles are associated with prostate cancer susceptibility and influence gene expression. BMC Cancer 2010;10:393.

69. Chen H, Chen Y, Zhao Y, Fan W, Zhou K, Liu Y, et al. Association of sequence variants on chromosomes 20, 11, and 5 (20q13.33, 11q23.3, and 5p15.33) with glioma susceptibility in a Chinese population. Am J Epidemiol 2011;173:915-22.

70. Egan KM, Thompson RC, Nabors LB, Olson JJ, Brat DJ, Larocca RV, et al. Cancer susceptibility variants and the risk of adult glioma in a US case-control study. J Neurooncol 2011;104:535-42.

71. Gago-Dominguez M, Jiang X, Conti DV, Castelao JE, Stern MC, Cortessis VK, et al. Genetic variations on chromosomes 5p15 and 15q25 and bladder cancer risk: findings from the Los Angeles-Shanghai bladder case-control study. Carcinogenesis 2011;32:197-202.

72. Hofer P, Baierl A, Feik E, Fuhrlinger G, Leeb G, Mach K, et al. MNS16A tandem repeats minisatellite of human telomerase gene: a risk factor for colorectal cancer. Carcinogenesis 2011;32:866-71.

73. Hu Z, Wu C, Shi Y, Guo H, Zhao X, Yin Z, et al. A genome-wide association study identifies two new lung cancer susceptibility loci at 13q12.12 and 22q12.2 in Han Chinese. Nat Genet 2011;43:792-6.

74. Jin G, Yoo SS, Cho S, Jeon HS, Lee WK, Kang HG, et al. Dual roles of a variable number of tandem repeat polymorphism in the TERT gene in lung cancer. Cancer Sci 2011;102:144-9.

75. Nan H, Qureshi AA, Prescott J, De Vivo I, Han J. Genetic variants in telomere-maintaining genes and skin cancer risk. Hum Genet 2011;129:247-53.

76. Kanetsky PA, Mitra N, Vardhanabhuti S, Vaughn DJ, Li M, Ciosek SL, et al. A second independent locus within DMRT1 is associated with testicular germ cell tumor susceptibility. Hum Mol Genet 2011;20:3109-17.

77. Kohno T, Kunitoh H, Mimaki S, Shiraishi K, Kuchiba A, Yamamoto S, et al. Contribution of the TP53, OGG1, CHRNA3, and HLA-DQA1 genes to the risk for lung squamous cell carcinoma. J Thorac Oncol 2011;6:813-7.

78. Kote-Jarai Z, Olama AA, Giles GG, Severi G, Schleutker J, Weischer M, et al. Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study. Nat Genet 2011;43:785-91.

79. Kratz CP, Han SS, Rosenberg PS, Berndt SI, Burdett L, Yeager M, et al. Variants in or near KITLG, BAK1, DMRT1, and TERT-CLPTM1L predispose to familial testicular germ cell tumour. J Med Genet 2011;48:473-6.

80 Pande M, Spitz MR, Wu X, Gorlov IP, Chen W, Amos CI. Novel genetic variants in the chromosome 5p15.33 region associate with lung cancer risk. Carcinogenesis 2011.

81. Peters U, Hutter CM, Hsu L, Schumacher FR, Conti DV, Carlson CS, et al. Meta-analysis of new genome-wide association studies of colorectal cancer risk. Hum Genet 2011.

82. Wang K, Diskin SJ, Zhang H, Attiyeh EF, Winter C, Hou C, et al. Integrative genomics identifies LMO1 as a neuroblastoma oncogene. Nature 2011;469:216-20.

83. Wauters E, Smeets D, Coolen J, Verschakelen J, De Leyn P, Decramer M, et al. The TERT-CLPTM1L locus for lung cancer predisposes to bronchial obstruction and emphysema. Eur Respir J 2011.

84. Young RP, Hopkins RJ, Whittington CF, Hay BA, Epton MJ, Gamble GD. Individual and cumulative effects of GWAS susceptibility loci in lung cancer: associations after sub-phenotyping for COPD. PLoS One 2011;6:e16476.

85. Taylor J, Tyekucheva S, King DC, Hardison RC, Miller W, Chiaromonte F. ESPERR: learning strong and weak signals in genomic sequence alignments to identify functional elements. Genome Res 2006;16:1596-604.

86. Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet 2009;84:52-9.

87. Mirabello L, Yu K, Kraft P, De Vivo I, Hunter DJ, Prescott J, et al. The association of telomere length and genetic variation in telomere biology genes. Hum Mutat 2010;31:1050-8.

88. Perona R, Machado-Pinilla R, Manguan C, Carrillo J. Telomerase deficiency and cancer susceptibility syndromes. Clin Transl Oncol 2009;11:711-4.

89. Yamamoto K, Okamoto A, Isonishi S, Ochiai K, Ohtake Y. A novel gene, CRR9, which was up-regulated in CDDP-resistant ovarian tumor cell line, was associated with apoptosis. Biochem Biophys Res Commun 2001;280:1148-54.

90. Webb E, Broderick P, Lubbe S, Chandler I, Tomlinson I, Houlston RS. A genome-wide scan of 10 000 gene-centric variants and colorectal cancer risk. Eur J Hum Genet 2009;17:1507-14.

91. Han J, Qureshi AA, Prescott J, Guo Q, Ye L, Hunter DJ, et al. A prospective study of telomere length and the risk of skin cancer. J Invest Dermatol 2009;129:415-21.

92. Bataille V, Kato BS, Falchi M, Gardner J, Kimura M, Lens M, et al. Nevus size and number are associated with telomere length and represent potential markers of a decreased senescence in vivo. Cancer Epidemiol Biomarkers Prev 2007;16:1499-502.

93. Mocellin S, Nitti D. Cutaneous melanoma in situ: translational evidence from a large population-based study. Oncologist 2011;16:896-903.

94. Riethman H. Human telomere structure and biology. Annu Rev Genomics Hum Genet 2008;9:1-19.

CONTEXT AND CAVEATS

Prior knowledge

Previous studies have provided abundant evidence that polymorphisms in the telomerase reverse transcriptase (*TERT*) gene are associated with cancer development, but a comprehensive synopsis is currently not available.

Study design

Publications in English were searched for associations between TERT locus polymorphisms and risk of cancer. A systematic review and meta-analysis of literature was conducted to assess the cumulative evidence for associations according to the Venice criteria. Because *TERT* locus also includes the cleft lip and palate transmembrane 1-like (*CLPTM1L*) gene, *CLPTM1L* polymorphisms were also analyzed.

Contribution

Eighty-five studies contributed data for 67 *TERT* locus polymorphisms from 24 tumor types for a total of 221 unique combinations of polymorphisms and cancer types. Meta-analysis showed that 22 polymorphisms were associated with risk of at least one cancer type. Cumulative evidence for associations with at least one tumor type was strong for 11 polymorphisms.

Implications

This synopsis confirms that genetic variation in the *TERT* locus can modulate cancer risk.

Limitations

Some publications may have been overlooked. For some polymorphisms and tumors, data were insufficient for pooling.