

# Multiple independent variants at the *TERT* locus are associated with telomere length and risks of breast and ovarian cancer

*TERT*-locus SNPs and leukocyte telomere measures are reportedly associated with risks of multiple cancers. Using the Illumina custom genotyping array iCOGs, we analyzed ~480 SNPs at the *TERT* locus in breast ( $n = 103,991$ ), ovarian ( $n = 39,774$ ) and *BRCA1* mutation carrier ( $n = 11,705$ ) cancer cases and controls. Leukocyte telomere measurements were also available for 53,724 participants. Most associations cluster into three independent peaks. The minor allele at the peak 1 SNP rs2736108 associates with longer telomeres ( $P = 5.8 \times 10^{-7}$ ), lower risks for estrogen receptor (ER)-negative ( $P = 1.0 \times 10^{-8}$ ) and *BRCA1* mutation carrier ( $P = 1.1 \times 10^{-5}$ ) breast cancers and altered promoter assay signal. The minor allele at the peak 2 SNP rs7705526 associates with longer telomeres ( $P = 2.3 \times 10^{-14}$ ), higher risk of low-malignant-potential ovarian cancer ( $P = 1.3 \times 10^{-15}$ ) and greater promoter activity. The minor alleles at the peak 3 SNPs rs10069690 and rs2242652 increase ER-negative ( $P = 1.2 \times 10^{-12}$ ) and *BRCA1* mutation carrier ( $P = 1.6 \times 10^{-14}$ ) breast and invasive ovarian ( $P = 1.3 \times 10^{-11}$ ) cancer risks but not via altered telomere length. The cancer risk alleles of rs2242652 and rs10069690, respectively, increase silencing and generate a truncated *TERT* splice variant.

Chromosome ends are capped by telomeres, which protect them from inappropriate DNA repair and maintain genomic integrity<sup>1</sup>. Telomeres consist of structural proteins<sup>2</sup> combined with many hundreds of hexanucleotide DNA repeats<sup>3,4</sup>, which are progressively shortened by normal cell division<sup>5-7</sup>. Shortening restricts the proliferation of normal somatic cells but not cancer cells, which can maintain long telomeres, usually via telomerase<sup>8-10</sup>, and may divide indefinitely. The *TERT* gene at 5p15.33 (NCBI gene 7015) encodes the catalytic subunit of telomerase reverse transcriptase, a key component of telomerase. Germline mutations in *TERT* cause dyskeratosis congenita, a cancer susceptibility disorder characterized by exceedingly short telomeres<sup>11</sup>. Although up to 80% of the variation of telomere length is estimated to be due to heritable factors<sup>12,13</sup>, association studies of *TERT* SNPs and differences in leukocyte telomere length have so far been inconclusive<sup>14-17</sup>. Furthermore, it is unclear whether telomere length, measured in leukocyte DNA, is predictive of cancer risk: retrospective studies report that cancer patients after diagnosis have shorter telomeres than unaffected controls<sup>18-21</sup>, but prospective studies with DNA taken before diagnosis have been inconclusive<sup>19,22,23</sup>. SNPs at 5p15.33 are reported to be associated with risks of several human cancers<sup>14-16,24-32</sup>, including certain subtypes of both ovarian<sup>33</sup> and breast<sup>34</sup> cancers.

Resulting from a common interest, members of each of the constituent consortia in the Collaborative Oncological Gene-environment Study (COGS) nominated SNPs surrounding the *TERT* locus for inclusion on a genotyping array. Consequently, the iCOGS array design included a combination of individual *TERT* gene candidate SNPs, as well as a more comprehensive set to fine-scale map the entire locus, for shared use by all consortia. This study had three aims:

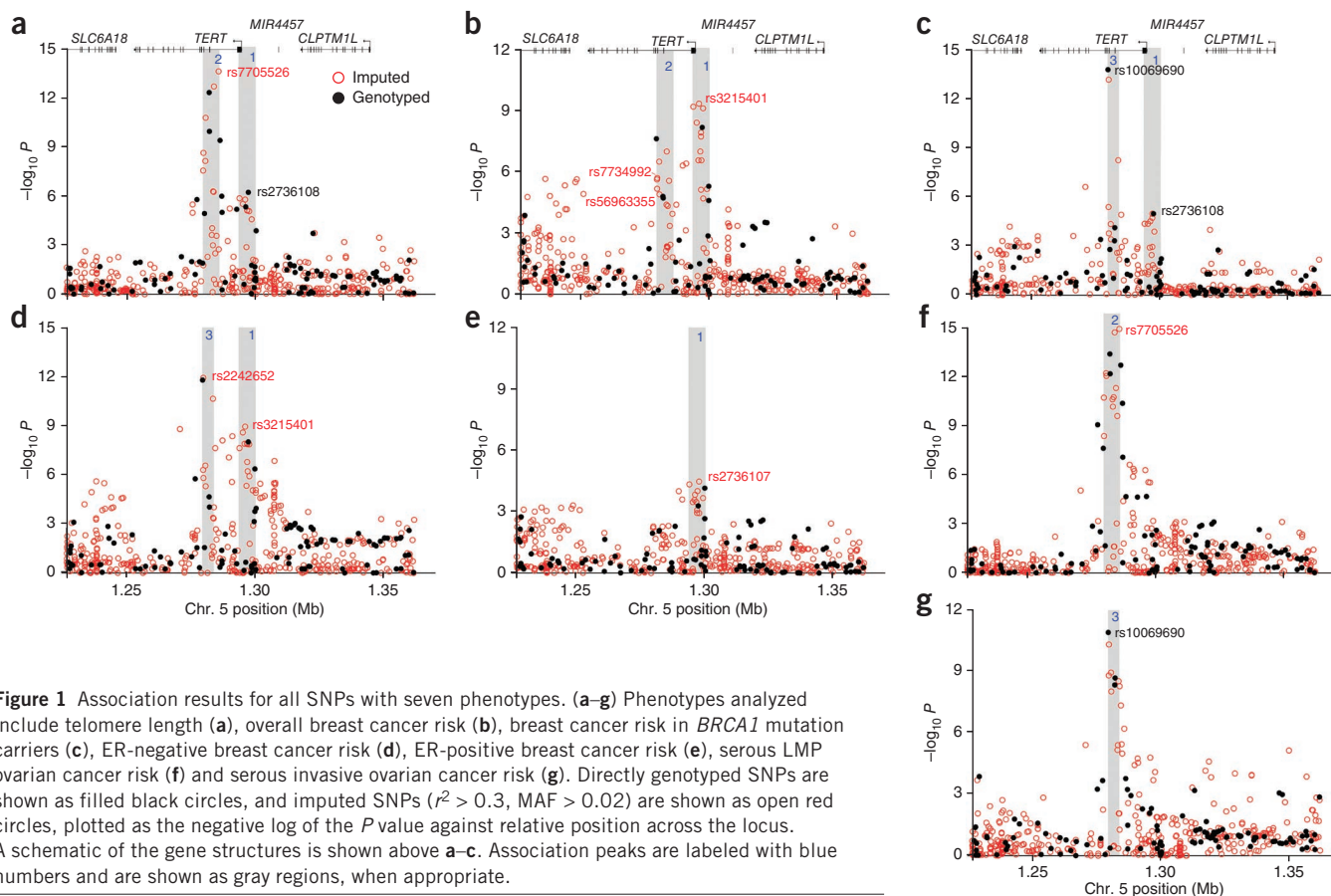
to assess SNPs across the *TERT* locus for all detectable associations with mean telomere length and breast and ovarian cancer subtypes; to fine-scale map this locus to identify potentially causal variants for the observed associations; and to evaluate the functional effects of the strongest candidate causative variants.

## RESULTS

One hundred and ten SNPs at the 5p15.33 locus (Build 37 positions 1,227,693–1,361,969) passed quality control tests in 103,991 breast cancer cases and controls from 52 Breast Cancer Association Consortium (BCAC) studies, of which 41 studies (89,050 individuals) were of European ancestry, 9 were of Asian ancestry (12,893 individuals) and 2 were of African-American ancestry (2,048 individuals). The same 110 SNPs passed quality control tests in 11,705 *BRCA1* mutation carriers of European ancestry, recruited by 45 studies from the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA), and 108 SNPs passed quality control tests in 44,308 ovarian cancer cases and controls from 43 Ovarian Cancer Association Consortium (OCAC) studies. For OCAC, analysis was confined to the 39,774 participants of European ancestry, of whom 8,371 cases had invasive epithelial ovarian neoplasia and 986 had serous low-malignant-potential (LMP) neoplasia. For all study participants, genotype imputation, using the 110 genotyped SNPs together with the January 2012 release of the 1000 Genomes Project<sup>35-38</sup>, was used to increase coverage to ~480 SNPs (imputation  $r^2 > 0.3$ ; minor allele frequency (MAF)  $> 0.02$ ) for each phenotype. Telomere length was initially measured in control subjects from two BCAC studies (Studies of Epidemiology And Risk factors in Cancer Heredity (SEARCH) and the Copenhagen City Heart Study (CCHS); combined  $n = 15,567$ ) (**Supplementary Note**).

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**Figure 1** Association results for all SNPs with seven phenotypes. (a–g) Phenotypes analyzed include telomere length (a), overall breast cancer risk (b), breast cancer risk in *BRCA1* mutation carriers (c), ER-negative breast cancer risk (d), ER-positive breast cancer risk (e), serous LMP ovarian cancer risk (f) and serous invasive ovarian cancer risk (g). Directly genotyped SNPs are shown as filled black circles, and imputed SNPs ( $r^2 > 0.3$ , MAF  $> 0.02$ ) are shown as open red circles, plotted as the negative log of the  $P$  value against relative position across the locus. A schematic of the gene structures is shown above a–c. Association peaks are labeled with blue numbers and are shown as gray regions, when appropriate.

Manhattan plots are shown of the genotyped and well-imputed SNPs for the seven phenotypes analyzed, including mean telomere length (Fig. 1a), overall breast cancer risk (Fig. 1b), breast cancer in *BRCA1* mutation carriers (Fig. 1c), ER-negative breast cancer (Fig. 1d), ER-positive breast cancer (Fig. 1e), serous LMP ovarian cancer (Fig. 1f) and serous invasive ovarian cancer (Fig. 1g). Conditional analyses within each of these phenotypes identified multiple independent SNP associations each for telomere length, overall breast cancer risk, ER-negative breast cancer and breast cancer in *BRCA1* mutation carriers but only one peak each for ER-positive breast cancer, serous LMP ovarian cancer and invasive ovarian cancer (Table 1). Full results of all these SNP analyses are given in Supplementary Tables 1–3. All associations are consistent with a log-additive model.

### Associations with telomere length

SNPs in two distinct regions (hereafter denoted peaks 1 and 2) were strongly associated with telomere length (Fig. 1a, Tables 1 and 2 and Supplementary Fig. 1a). Imputed SNP rs7705526 (peak 2, position 1,285,974, *TERT* intron 2) had the largest effect, with a change in relative telomere length of 1.026-fold per allele (95% confidence interval (CI) = 1.019–1.033;  $P = 2.3 \times 10^{-14}$ ; conditional  $P = 2.5 \times 10^{-11}$ ). We confirmed this finding in an additional 20,512 women and 17,645 men from a third study (CGPS) genotyped for rs7726159 (the best directly genotyped SNP;  $r^2 = 0.83$  with rs7705526). From a joint analysis of all 53,724 individuals, the change in relative telomere length was 1.020-fold per allele (95% CI = 1.016–1.023;  $P = 7.5 \times 10^{-28}$ ). A second, independent association was observed with rs2736108 (peak 1, position 1,297,488, *TERT* promoter) with a per-allele change in relative telomere length of 1.017-fold (95% CI = 1.010–1.024;

$P = 5.8 \times 10^{-7}$ ; conditional  $P = 4.0 \times 10^{-4}$ ) (Fig. 1a, Tables 1 and 2 and Supplementary Fig. 1a). SNPs rs7705526 and rs2736108 were only weakly correlated ( $r^2 = 0.04$  in Europeans). Weak associations between peak 3 SNPs and telomere length became nonsignificant after adjustment for peak 2 SNP rs7705526 (data not shown).

### Associations with breast cancer risk

We identified SNPs associated with breast cancer risk ( $P < 1 \times 10^{-4}$ ) in three distinct regions in subjects from the BCAC studies and in two regions in CIMBA *BRCA1* mutation carriers. No significant ( $P < 1 \times 10^{-4}$ ) evidence for heterogeneity among odds ratios (ORs) or hazard ratios (HRs) between studies for any of the top SNPs was observed (Supplementary Fig. 2). The strongest association with overall breast cancer risk in BCAC was with peak 1 SNP rs3215401 (Fig. 1b, Tables 1 and 2 and Supplementary Fig. 1b). There was also good evidence for an association with SNPs in peak 2 and weaker evidence that an additional SNP, outside the three main association peaks, was independently associated with breast cancer risk (Table 1 and Supplementary Table 1). The most strongly associated SNPs in *BRCA1* mutation carriers were located in introns 2–4 (hereafter denoted peak 3), including rs10069690 (Fig. 1c, Tables 1 and 2 and Supplementary Fig. 2c) and rs2242652 (correlation with rs10069690,  $r^2 = 0.70$ ). The latter SNP also showed the strongest association with ER-negative breast cancer in BCAC (Fig. 1d, Tables 1 and 2 and Supplementary Fig. 1d) but showed little evidence of association with ER-positive breast cancer (Table 2). Stepwise regression analysis in CIMBA studies indicated two independent associations with breast cancer risk in *BRCA1* mutation carriers (conditional  $P = 5 \times 10^{-5}$  for rs2736108 in peak 1 and  $P = 4.8 \times 10^{-13}$  for rs10069690 in peak 3).

**Table 1** Independently associated SNPs for each phenotype

	SNP	Chr. 5 position	<i>TERT</i> peak	Source	Effect (95% CI)	$P_{\text{trend}}$
<b>Telomere length (RTL)</b>						
BCAC (SEARCH and CCHS)						
$n = 15,567$	rs2736108	1,297,488	1	Genotyped	1.010 (1.004–1.016)	0.0004
	rs7705526	1,285,974	2	Imputed	1.019 (1.014–1.025)	$2.47 \times 10^{-11}$
<b>Overall breast cancer</b>						
BCAC						
46,451 cases, 42,599 controls	rs3215401	1,296,255	1	Imputed	0.94 (0.91–0.96)	$9.91 \times 10^{-10}$
	rs7734992	1,280,128	2	Imputed	1.06 (1.04–1.08)	$1.73 \times 10^{-7}$
	rs56963355	1,251,503	None	Imputed	0.90 (0.84–0.95)	$1.95 \times 10^{-5}$
<b>Risk of breast cancer in <i>BRCA1</i>-mutation carriers</b>						
CIMBA						
$n = 11,705$	rs2736108	1,297,488	1	Genotyped	0.92 (0.88–0.96)	$5.12 \times 10^{-5}$
	rs10069690	1,279,790	3	Genotyped	1.16 (1.11–1.21)	$4.83 \times 10^{-13}$
<b>Estrogen receptor–negative breast cancer</b>						
BCAC						
7,435 cases, 41,575 controls	rs3215401	1,296,255	1	Imputed	0.91 (0.86–0.95)	$6.15 \times 10^{-6}$
	rs2242652	1,280,028	3	Imputed	1.15 (1.10–1.20)	$4.29 \times 10^{-9}$
<b>Estrogen receptor–positive breast cancer</b>						
BCAC						
27,074 cases, 41,749 controls	rs2736107	1,297,854	1	Imputed	0.95 (0.92–0.97)	$3.32 \times 10^{-5}$
<b>Serous LMP ovarian cancer</b>						
OCAC						
986 cases, 23,491 controls	rs7705526	1,285,974	2	Imputed	1.51 (1.36–1.67)	$1.34 \times 10^{-15}$
<b>Serous invasive ovarian cancer</b>						
OCAC						
8,371 cases, 23,491 controls	rs10069690	1,279,790	3	Genotyped	1.15 (1.11–1.20)	$1.25 \times 10^{-11}$

Independently associated SNPs are shown for each phenotype, including overall breast cancer and ER subgroups in European individuals in BCAC and invasive and LMP subgroups in OCAC following forward conditional stepwise logistic regression analysis, relative change in telomere length in SEARCH and CCHS combined data following forward stepwise linear regression analysis and breast cancer in *BRCA1* mutation carriers in CIMBA following forward stepwise Cox regression. These analyses were performed on all SNPs with MAF > 0.02 and association  $P < 1 \times 10^{-4}$  in the single-SNP analyses.

A very similar pattern was observed for ER-negative breast cancer in BCAC (conditional  $P = 6 \times 10^{-6}$  for rs3215401 in peak 1 and  $P = 4.3 \times 10^{-9}$  for rs2242652 in peak 3; **Table 1**).

The most strongly associated SNP with ER-positive breast cancer was rs2736107 in peak 1 (**Fig. 1e**, **Tables 1** and **2** and **Supplementary Fig. 3e**). Weak associations between the key SNPs and risk for *BRCA2* mutation carriers were also observed, but the sample size was too small to draw definitive conclusions (data not shown).

### Associations with ovarian cancer risk

The strongest association observed for risk of LMP ovarian cancer was with peak 2 SNP rs7705526, and this was the only SNP retained in the stepwise regression analysis (**Fig. 1f**, **Tables 1** and **2** and **Supplementary Fig. 1f**). The strongest observed association for serous invasive ovarian cancer was with peak 3 SNP rs10069690 (**Fig. 1g**, **Tables 1** and **2** and **Supplementary Fig. 1g**). No other independent association was observed for serous invasive ovarian cancer (**Table 1**). We also analyzed SNP associations with endometrioid, mucinous, clear-cell invasive and mucinous LMP ovarian cancers but found no associations at  $P < 1 \times 10^{-4}$  (**Supplementary Table 4**). We attempted analysis of invasive serous ovarian cancer stratified by grade, but, again, statistical power was low (**Supplementary Fig. 3**).

### Three main peaks of association within the *TERT* locus

The above results indicate that the majority of observed associations with all seven tested phenotypes fall into association peaks 1–3.

Correlated SNPs in the *TERT* promoter (peak 1) were associated with telomere length, ER-positive breast cancer, ER-negative breast cancer and breast cancer in *BRCA1* mutation carriers. SNPs in peak 2, spanning *TERT* introns 2–4, were independently associated with telomere length, overall breast cancer risk and serous LMP ovarian cancer. SNPs in peak 3, also spanning *TERT* introns 2–4, showed strong associations with ER-negative breast cancer, breast cancer risk for *BRCA1* mutation carriers and serous invasive ovarian cancer but not with telomere length (**Tables 1** and **2**). Although peaks 2 and 3 overlap physically, they define distinct sets of SNPs that are only partially correlated (for example, correlation between rs10069690 and rs7705526 was weak,  $r^2 = 0.33$ ; **Fig. 2**). Some SNP-phenotype associations in peak 2 were clearly weaker than those in peak 3 (for example, with ER-negative breast cancer) and became nonsignificant after adjustment for SNP rs2242652 in peak 3. Conversely, the associations with telomere length and serous LMP ovarian cancer were stronger for SNPs in peak 2, indicating that the associations in peaks 2 and 3 are not being driven by the same causal variants.

The strongest candidates for causation within each peak were identified by computing likelihood ratios; the SNPs listed in **Tables 1** and **2** are those that cannot be excluded from being causal candidates at a likelihood ratio of >1:100 fold compared to the top hit in the peak. The statistical power to exclude SNPs differed between phenotypes: in peak 1, all but seven SNPs could be excluded from being causal for relative telomere length, breast cancer risk in *BRCA1* mutation carriers and ER-negative breast cancer risk, but an additional SNP could be excluded for

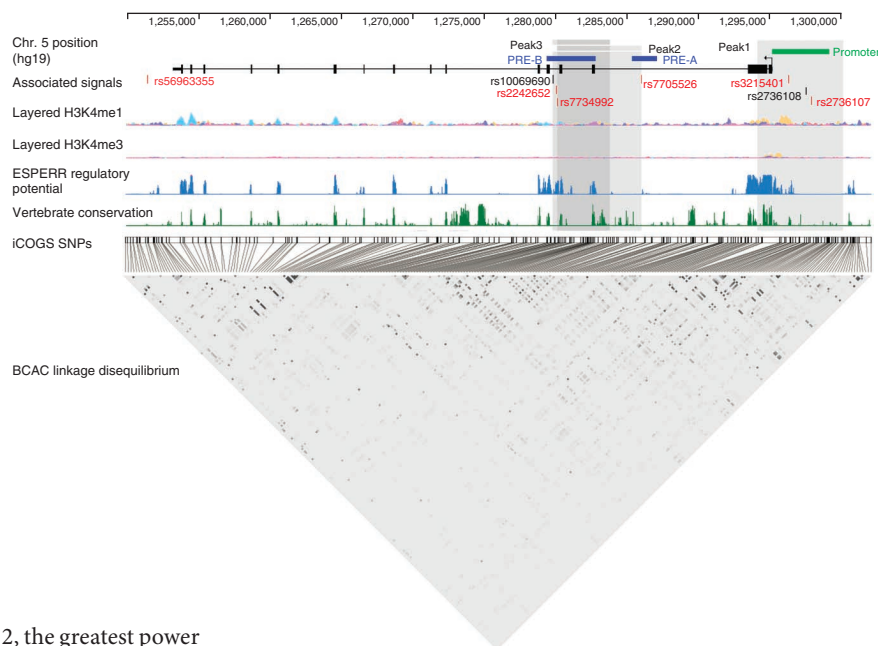
Table 2 Association between *TERT* SNPs and the seven studied phenotypes

SNP	Chr. 5 position	Major/minor allele	MAF	Telomere length change		Overall breast cancer risk		Risk of breast cancer in <i>BRCA1</i> mutation carriers		ER-negative breast cancer risk		ER-positive breast cancer risk		Serous LMP ovarian cancer risk		Serous invasive epithelial ovarian cancer risk	
				RTL (95% CI)	$P_{\text{trend}}$	OR (95% CI)	$P_{\text{trend}}$	HR (95% CI)	$P_{\text{trend}}$	OR (95% CI)	$P_{\text{trend}}$	OR (95% CI)	$P_{\text{trend}}$	OR (95% CI)	$P_{\text{trend}}$	OR (95% CI)	$P_{\text{trend}}$
<b>Peak 1: promoter</b>																	
rs7736107	1,297,854	C/T	0.28	1.015 (1.009–1.022)	$8.33 \times 10^{-7}$	0.93 (0.91–0.96)	$7.95 \times 10^{-10}$	0.90 (0.86–0.95)	0.00013	0.88 (0.83–0.93)	$1.41 \times 10^{-8}$	<b>0.95</b> <b>(0.92–0.97)<sup>b</sup></b>	$3.32 \times 10^{-5}$	1.01 (0.91–1.11)	0.909	0.98 (0.94–1.02)	0.301
rs2736108 <sup>a</sup>	1,297,488	C/T	0.29	<b>1.017</b> <b>(1.010–1.024)<sup>b</sup></b>	$5.81 \times 10^{-7}$	0.94 (0.92–0.95)	$6.73 \times 10^{-9}$	0.89 (0.85–0.94) <sup>b</sup>	$1.05 \times 10^{-5}$	0.89 (0.84–0.93)	$1.01 \times 10^{-8}$	0.96 (0.93–0.98)	0.00051	1.00 (0.91–1.10)	0.996	0.98 (0.94–1.02)	0.238
rs27525896	1,297,081	CCAC	0.27	1.016 (1.009–1.023)	$7.13 \times 10^{-6}$	0.94 (0.92–0.96)	$1.20 \times 10^{-8}$	<b>0.88</b> <b>(0.84–0.93)</b>	<b><math>1.04 \times 10^{-5}</math></b>	0.88 (0.84–0.92)	$1.21 \times 10^{-8}$	0.96 (0.93–0.98)	0.00083	1.02 (0.92–1.13)	0.762	0.98 (0.94–1.02)	0.324
5-1297077	1,297,077	ACC/A	0.27	1.016 (1.009–1.023)	$7.13 \times 10^{-6}$	0.94 (0.92–0.96)	$1.91 \times 10^{-8}$	0.89 (0.84–0.94)	$1.90 \times 10^{-5}$	0.88 (0.84–0.93)	$1.37 \times 10^{-8}$	0.96 (0.93–0.98)	0.00051	1.02 (0.92–1.13)	0.769	0.98 (0.94–1.02)	0.351
rs3215401	1,296,255	A/AG	0.30	1.016 (1.009–1.023)	$1.63 \times 10^{-6}$	<b>0.94</b> <b>(0.91–0.96)<sup>b</sup></b>	<b><math>4.68 \times 10^{-10}</math></b>	0.90 (0.85–0.94)	$3.05 \times 10^{-5}$	<b>0.88</b> <b>(0.84–0.92)<sup>b</sup></b>	<b><math>1.19 \times 10^{-9}</math></b>	0.95 (0.93–0.98)	0.0012	1.01 (0.91–1.11)	0.908	0.98 (0.94–1.01)	0.188
rs2853669	1,295,349	A/G	0.30	1.016 (1.009–1.024)	$2.95 \times 10^{-6}$	0.94 (0.92–0.96)	$4.01 \times 10^{-9}$	0.90 (0.85–0.94)	$4.26 \times 10^{-5}$	0.88 (0.84–0.92)	$2.60 \times 10^{-9}$	0.96 (0.93–0.98)	0.00034	1.01 (0.91–1.11)	0.893	0.97 (0.94–1.01)	0.204
rs2736098	1,294,086	C/T	0.27	1.017 (1.010–1.024)	$1.35 \times 10^{-6}$	0.93 (0.91–0.96)	$6.65 \times 10^{-10}$	0.89 (0.85–0.94)	$4.22 \times 10^{-5}$	0.88 (0.84–0.93)	$2.41 \times 10^{-8}$	0.95 (0.92–0.97)	$4.58 \times 10^{-5}$	1.00 (0.91–1.11)	0.935	0.97 (0.93–1.01)	0.152
<b>Peak 2: introns 2–4</b>																	
rs7705526	1,285,974	C/A	0.33	<b>1.026</b> <b>(1.019–1.033)<sup>b</sup></b>	$2.32 \times 10^{-14}$	1.04 (1.02–1.06)	0.00011	1.04 (0.99–1.10)	0.120	1.06 (1.02–1.10)	0.0035	1.04 (1.01–1.06)	0.0049	<b>1.51</b> <b>(1.36–1.67)<sup>b</sup></b>	<b><math>1.34 \times 10^{-15}</math></b>	1.11 (1.06–1.15)	$6.38 \times 10^{-7}$
rs4449583	1,284,135	C/T	0.34	1.025 (1.018–1.031)	$1.93 \times 10^{-13}$	1.04 (1.02–1.06)	$4.75 \times 10^{-5}$	1.08 (1.03–1.14)	0.002	1.08 (1.04–1.12)	$9.68 \times 10^{-5}$	1.03 (1.01–1.06)	0.014	1.49 (1.35–1.64)	$2.18 \times 10^{-15}$	1.13 (1.08–1.17)	$5.38 \times 10^{-9}$
rs7725218 <sup>a</sup>	1,282,414	G/A	0.35	1.021 (1.015–1.028)	$1.10 \times 10^{-10}$	1.04 (1.02–1.06)	$1.95 \times 10^{-5}$	1.10 (1.05–1.16)	$7.47 \times 10^{-5}$	1.08 (1.04–1.12)	$9.29 \times 10^{-5}$	1.03 (1.01–1.06)	0.0083	1.42 (1.29–1.56)	$7.24 \times 10^{-13}$	1.12 (1.08–1.17)	$2.08 \times 10^{-9}$
rs7726159 <sup>a</sup>	1,282,319	C/A	0.34	1.024 (1.017–1.031)	$4.52 \times 10^{-13}$	1.05 (1.03–1.07)	$1.29 \times 10^{-5}$	1.09 (1.04–1.15)	0.00047	1.09 (1.05–1.13)	$2.23 \times 10^{-5}$	1.03 (1.01–1.06)	0.0090	1.44 (1.31–1.59)	$4.50 \times 10^{-14}$	1.12 (1.08–1.17)	$4.59 \times 10^{-9}$
5-1280940	1,280,940	GAG CCA CCG	0.37	1.023 (1.016–1.029)	$1.62 \times 10^{-11}$	1.05 (1.03–1.07)	$1.62 \times 10^{-5}$	1.10 (1.04–1.15)	0.00038	1.10 (1.06–1.14)	$5.02 \times 10^{-6}$	1.03 (1.00–1.05)	0.021	1.44 (1.30–1.59)	$9.83 \times 10^{-13}$	1.12 (1.08–1.17)	$9.45 \times 10^{-9}$
rs7734992	1,280,128	T/C	0.43	1.019 (1.013–1.025)	$2.23 \times 10^{-9}$	<b>1.05</b> <b>(1.03–1.07)<sup>b</sup></b>	<b><math>2.06 \times 10^{-6}</math></b>	1.10 (1.05–1.15)	0.00017	1.10 (1.06–1.14)	$1.57 \times 10^{-6}$	1.03 (1.01–1.06)	0.0053	1.45 (1.31–1.59)	$5.25 \times 10^{-14}$	1.12 (1.08–1.16)	$2.75 \times 10^{-9}$
<b>Peak 3: introns 2–4</b>																	
rs72709458	1,283,755	C/T	0.22	1.012 (1.005–1.020)	0.0010	1.07 (1.04–1.09)	$1.02 \times 10^{-7}$	1.19 (1.12–1.25)	$5.61 \times 10^{-9}$	1.17 (1.12–1.21)	$2.34 \times 10^{-11}$	1.04 (1.01–1.06)	0.014	1.45 (1.30–1.61)	$1.96 \times 10^{-11}$	1.15 (1.10–1.20)	$3.04 \times 10^{-9}$
rs2242652	1,280,028	G/A	0.20	1.009 (1.002–1.017)	0.016	1.06 (1.03–1.08)	$6.82 \times 10^{-6}$	1.25 (1.18–1.32)	$6.89 \times 10^{-14}$	<b>1.18</b> <b>(1.14–1.23)<sup>b</sup></b>	<b><math>1.23 \times 10^{-12}</math></b>	1.02 (0.99–1.05)	0.131	1.40 (1.25–1.56)	$4.45 \times 10^{-9}$	1.17 (1.12–1.22)	$4.85 \times 10^{-11}$
rs10069690 <sup>a</sup>	1,279,790	C/T	0.26	1.009 (1.002–1.016)	0.013	1.06 (1.04–1.08)	$2.43 \times 10^{-8}$	<b>1.23</b> <b>(1.16–1.29)<sup>b</sup></b>	<b><math>1.60 \times 10^{-14}</math></b>	1.16 (1.12–1.20)	$1.68 \times 10^{-12}$	1.03 (1.01–1.06)	0.011	1.33 (1.20–1.47)	$2.49 \times 10^{-8}$	<b>1.15</b> <b>(1.11–1.20)<sup>b</sup></b>	<b><math>1.25 \times 10^{-11}</math></b>

Single-SNP estimates for the most significant SNPs per peak per phenotype in the *TERT* fine-mapping region of chromosome 5 from positions 1,227,014 to 1,361,964 (Genome Build 37). The major and minor alleles are from the genotyping assay and are not necessarily from the coding strand. Change in telomere length per minor allele is given as fold change (RTL) with respect to the estimated telomere length for the common homozygote per SNP, both with 95% CI (**Supplementary Note**). All breast and ovarian cancer risk results are given as ORs with 95% CI and per-allele  $P_{\text{trend}}$ , and the risk results for *BRCA1* mutation carriers are given as HRs with 95% CI. All SNPs that cannot be excluded as >100x worse than the top hit in the block, using a likelihood ratio test, for any phenotype are listed. Independent peaks 1–3 were localized using forward conditional analyses (**Table 1**). The most significant hit in each region for each phenotype is shown in bold for each peak.

<sup>a</sup>Genotyped SNPs. All three peaks contain at least one directly genotyped variant. <sup>b</sup>Results for the most significant SNPs in each block in the forward conditional analyses (described further in **Table 1**).

**Figure 2** Associated signals within the *TERT* gene. Peak regions are labeled: peaks 2 and 3 overlap around introns 2–4, and peak 1 encompasses the promoter. The positions of associated SNPs are shown as black and red lines representing genotyped and imputed SNPs, respectively. The *TERT* gene structure is depicted with exons (boxes) joined by introns (lines). The positions of all analyzed iCOGS SNPs are marked. Data from the UCSC Genome Browser, including epigenetic marks for methylation of histone H3 at lysine 4 (H3K4me1) and trimethylation of histone H3 lysine 4 (H3K4me3), evolutionary and sequence pattern extraction through reduced representations (ESPERR) regulatory potential and vertebrate conservation tracks, are shown. Regions cloned into reporter constructs are depicted as the green rectangle (*TERT* promoter) or as blue rectangles (PRE-A and PRE-B). The pattern of linkage disequilibrium based on the BCAC population is shown with white representing  $r^2 = 0$  and black representing  $r^2 = 1$ .



ER-positive breast cancer risk (**Table 2**). In peak 2, the greatest power was for the telomere length phenotype, where all but three SNPs could be excluded, whereas five or six remained for cancer risk. For peak 3, three putative causal SNPs remained for ER-negative breast cancer risk, two for serous invasive ovarian cancer risk and just one for breast cancer risk in *BRCA1* mutation carriers. Results in each peak are compatible with a single causative variant being responsible for the multiple phenotype associations (notably, in peak 3, SNPs rs2242652 and rs10069690 were equally compatible with being the single causal variant). However, the possibilities of different causal variants being responsible for different phenotypes or of the associations being due to haplotype effects cannot be ruled out.

### Asian and African-American studies

We tested all SNPs ( $n = 341$ ) with MAF > 0.02 and imputation  $r^2 > 0.3$  for association with breast cancer in the 9 BCAC Asian studies (comprising 6,269 cases and 6,624 controls) for association, but none reached formal levels of significance. Furthermore, none of the top SNPs in individuals of European ancestry showed more than borderline levels of significance in Asians (**Supplementary Table 5**). Peak 3 SNP rs10069690 was directly genotyped in 2 BCAC African-American studies (1,116 cases and 932 controls), as well as in the above-mentioned Asian studies, and had estimated effects on ER-negative breast cancer similar to those in European populations (per-allele OR = 1.19, 95% CI = 1.06–1.31,  $P = 0.009$  in African-Americans and OR = 1.09, 95% CI = 1.00–1.19,  $P = 0.07$  in Asian women). Within OCAC, there were too few women of Asian and African ancestry to draw meaningful conclusions (**Supplementary Table 6**).

### Chromatin analysis

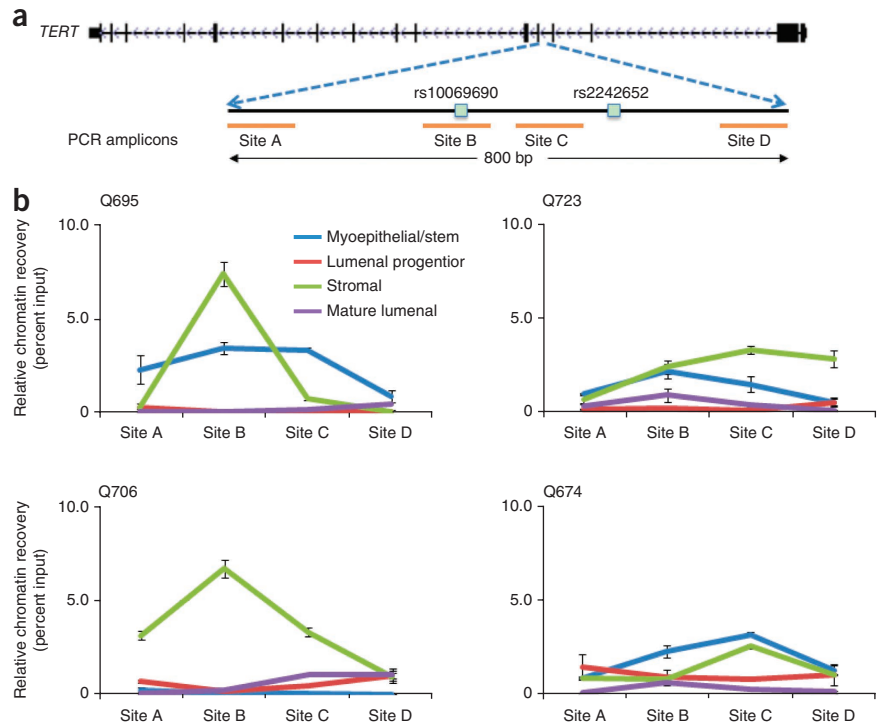
Analysis of Encyclopedia of DNA Elements (ENCODE) data<sup>39</sup> showed no evidence of regulatory elements or open chromatin coinciding with any risk-associated SNPs in normal breast epithelial cells or the other represented tissues (**Supplementary Fig. 4**). Data for ovarian tissues are not included in ENCODE. We therefore performed site-specific formaldehyde-assisted isolation of regulatory elements (FAIRE)<sup>40</sup> in ovarian cancer precursor tissues to identify regulatory elements in a 1 Mb region centered on peak 3. In fallopian tube secretory and ovarian surface epithelial cells, we detected FAIRE peaks coinciding with the *CLPTM1L* promoter but not the

*TERT* promoter (**Supplementary Fig. 4**). *In silico* analyses additionally indicated that *TERT* introns 4 and 5 (within and beyond peak 3) contained regions showing regulatory potential and vertebrate sequence conservation<sup>41</sup>. We performed site-specific FAIRE analyses on a ~1 kb region centered on the peak 3 SNP rs10069690 in normal tissue samples from breast reduction mammoplasty ( $n = 4$ ), ovarian cancer precursor tissues ( $n = 4$ ) and ovarian cancer cell lines ( $n = 4$ ). Breast cells from each woman were sorted into four enriched fractions on the basis of differential expression of cell surface markers<sup>42</sup> (myoepithelial/stem, luminal progenitor, mature luminal and stromal cells), and assays were performed on each fraction (**Fig. 3**). Chromatin was in a closed configuration in all ovarian, breast luminal progenitor and mature luminal cell fractions. However, in two of four stromal cell fractions, we detected ~600 bp of open chromatin of varying amplitude, covering the position of SNP rs10069690 but not of rs2242652, and, in three of four myoepithelial/stem cell fractions, we detected ~800 bp of open chromatin, covering the positions of both SNPs rs10069690 and rs2242652.

### Luciferase reporter assays

The regulatory capabilities of the DNA in each of the three peaks and the effects of most of the strongest candidate causative variants in each one were examined in luciferase reporter assays, using a construct containing 3,915 bp of the *TERT* promoter sequence<sup>43</sup>. The effects of peak 1 *TERT* promoter variants were examined via five haplotype constructs differing at rs2736107, rs2736108 and rs2736109 (ref. 25) (**Fig. 4a**): one with all three major alleles (wild-type *TERT*), another with all three minor alleles and three each with a single minor allele of the SNPs. Relative promoter activity was determined in ER-positive (MCF7) and ER-negative (MDA-MB-468) breast cancer cell lines and in an ovarian cancer cell line (A2780). The construct containing all three minor alleles consistently generated the lowest luciferase signals, close to baseline. To determine whether the risk-associated variants in peaks 2 and 3 fell within putative *cis*-acting regulatory elements (PREs), we cloned ~3 kb of sequence surrounding each SNP. Constructs of PRE-A (peak 2) had no significant effect on the activity of either the wild-type (*TERT*<sup>wt</sup>) promoter or the promoter with three minor alleles (*TER*<sup>th</sup>) (**Fig. 4a**). However, inclusion of the minor

**Figure 3** Open chromatin signatures around rs10069690. (a) Map of the PCR amplicon sites A–D used to annotate a 1 kb region surrounding rs10069690 and rs2242652. Primer sequences are listed in **Supplementary Table 11**. (b) PCR analysis of FAIRE-processed chromatin from FACS fractions enriched for myoepithelial/stem, luminal progenitor, mature luminal and stromal cells derived from the breast tissues of four subjects, Q695, Q723, Q706 and Q674. Error bars represent the standard errors from triplicate PCR runs.



allele of rs7705526 resulted in ~30% higher *TERT* promoter activity in all three cell lines, suggesting that it can act as a transcriptional enhancer. Higher promoter activity was also observed with this construct in A2780 ovarian cancer cells but not in the two breast cancer cell lines. Constructs of PRE-B (peak 3) consistently acted as strong transcriptional silencers, leading to 40–50% lower activity, specifically in constructs containing the wild-type *TERT* promoter. Notably, inclusion of the minor allele of rs2242652 in PRE-B constructs decreased relative wild-type *TERT* promoter activity by a further ~20% compared to the silencer containing the major allele, but the minor allele of the highly correlated SNP rs10069690 did not generate this effect (Fig. 4a).

### Alternative splicing of *TERT*

Several alternatively spliced variants of *TERT* have been found to affect telomerase activity<sup>44,45</sup>. To determine the role of PRE-B (peak 3) SNPs in *TERT* alternative splicing, we inserted intron 4 sequence into a full-length *TERT* cDNA mini-gene construct and confirmed accurate splicing. Cancer risk-associated alleles for rs10069690 and rs2242652 were generated individually and in combination within the mini-gene. RT-PCR, using primers spanning intron 4, showed that all SNP permutations in all cell lines produced comparable levels of both wild-type transcript and an INS1 alternatively spliced variant, which includes the first 38 bp of *TERT* intron 4 (refs. 46,47) (**Supplementary Fig. 5a**). We also identified a new splice variant of *TERT*, specifically associated with the minor allele of rs10069690 (termed INS1b; **Supplementary Fig. 5a**). Sequence analysis confirmed that INS1b includes the first 480 bp of intron 4 and results from the use of an alternative splice donor created by the minor allele of rs10069690 (ref. 48). INS1b has a premature stop codon 16 amino acids into intron 4 and is predicted to generate a severely truncated protein product, which is likely to affect telomerase activity (**Supplementary Fig. 5b**).

### Gene expression and methylation analyses in ovarian tissue

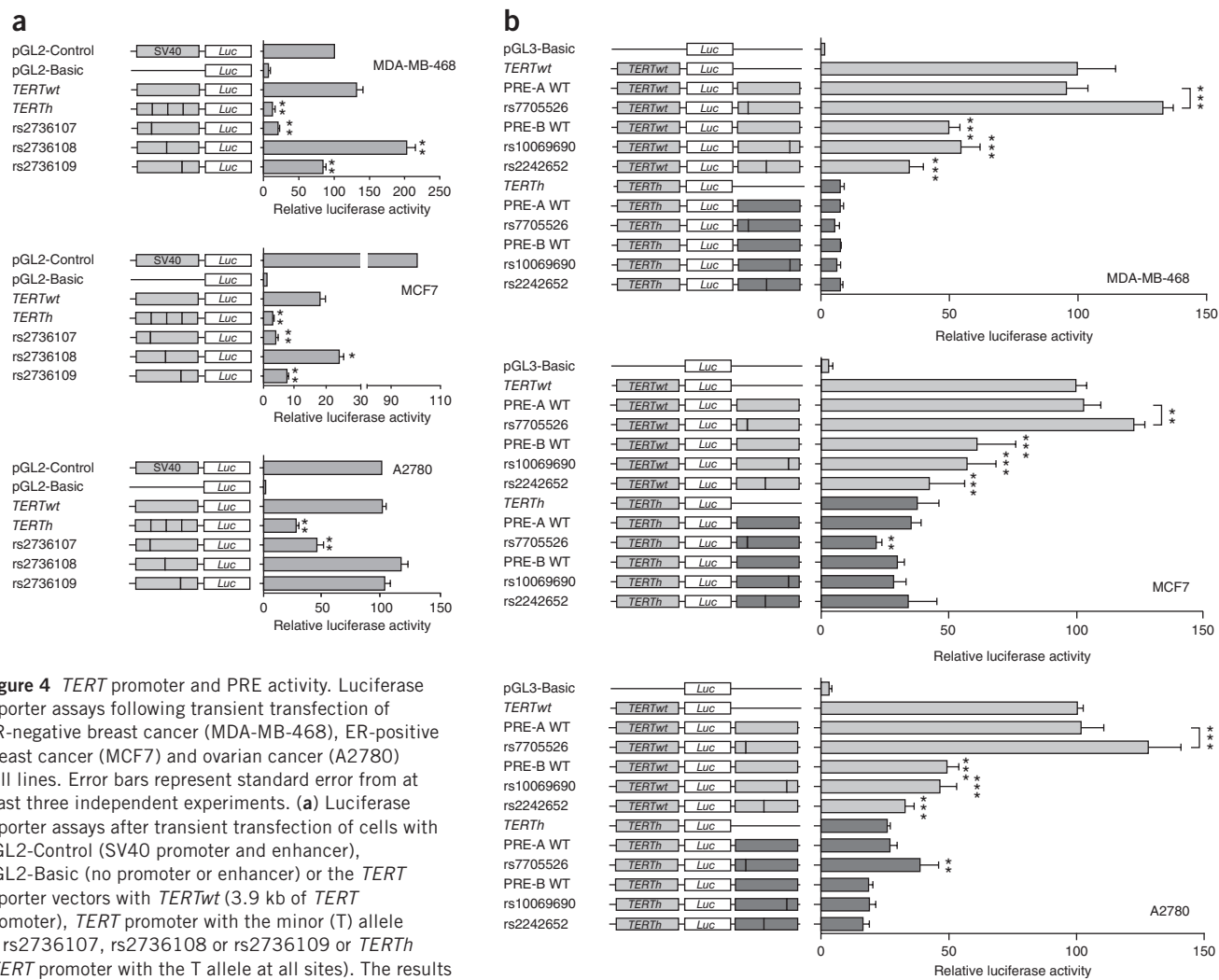
We used The Cancer Genome Atlas (TCGA)<sup>49</sup> data to examine gene expression of the 11 protein-coding genes and 1 microRNA (*MIR4457*) located within 1 Mb of peak 3 SNP rs10069690. Most genes showed higher expression in ovarian tumors compared with normal tissues (**Supplementary Fig. 4** and **Supplementary Table 7**). We observed no association between rs10069690 and the expression levels of any of the genes in any of the cells tested (**Supplementary Fig. 5** and **Supplementary Tables 7** and **8**). There was some evidence of association between rs10069690 and tumor methylation with probes cg23827991 (*TERT* CpG island,  $P = 1.3 \times 10^{-6}$ ) and

cg06550200 (*CLPTM1L*,  $P = 6.9 \times 10^{-4}$ ) out of the 935 probes tested. Both regions showed lower methylation with the minor, cancer risk-associated allele (**Supplementary Table 9**), but this did not correlate with changes in expression.

### DISCUSSION

Our comprehensive examination of the *TERT* locus has answered some long-standing questions and raised several new ones. We have identified two independent regions associated with telomere length in leukocyte DNA; these provide definitive evidence for genetic control of telomere length by common *TERT* variants. For rs2736108, the most significant SNP in promoter peak 1, the minor allele is associated with a 1.7% increase in telomere length. This is equal to a telomere length change of ~60 bp, which, because telomere length decreases by approximately 19 bp per year<sup>50</sup>, is equivalent in magnitude to an age difference of 3.1 years. We estimate that rs2736108 explains 0.08% of the variance in telomere length in men and 0.06% of the variation in women. SNPs in peak 2 have a stronger effect on telomere length, with each additional A (minor) allele of rs7705526 associated with a 2.6% increase. This is equal to a ~90 bp change in telomere length and, correspondingly, to 4.7 years of age. We estimate that rs7705526 explains 0.31% of the variance in telomere length in men and 0.16% of the variance in women. The only other reported associations with telomere length reaching genome-wide significance involve *TERC*-locus SNP rs1269304 (ref. 51) and *OBFC1*-locus SNP rs4387287 (ref. 52), which have similar effects on telomere length (75 bp and 115 bp per allele, respectively).

Our only findings consistent with the hypothesis that shorter telomeres predispose to increased cancer risk<sup>53</sup> (equivalent to longer telomeres being protective) are those from the peak 1 SNPs. However, a regulatory element construct containing the longer telomere-associated alleles of three highly correlated SNPs, rs2736108, rs2736107 and rs2736109 (reconstructing a haplotype with 25% frequency in Europeans<sup>35</sup>), virtually abolished promoter activity in a reporter assay. This finding leaves a seemingly paradoxical association



**Figure 4** *TERT* promoter and PRE activity. Luciferase reporter assays following transient transfection of ER-negative breast cancer (MDA-MB-468), ER-positive breast cancer (MCF7) and ovarian cancer (A2780) cell lines. Error bars represent standard error from at least three independent experiments. (a) Luciferase reporter assays after transient transfection of cells with pGL2-Control (SV40 promoter and enhancer), pGL2-Basic (no promoter or enhancer) or the *TERT* reporter vectors with *TERTwt* (3.9 kb of *TERT* promoter), *TERT* promoter with the minor (T) allele of rs2736107, rs2736108 or rs2736109 or *TERTth* (*TERT* promoter with the T allele at all sites). The results of comparisons with wild-type *TERT* performed using one-way ANOVA with *post-hoc* Dunnett's tests are shown (\*\* $P < 0.001$ , \* $P < 0.005$ ). (b) PRE-A or PRE-B was cloned downstream of either the *TERTwt* or *TERTth* promoter-driven reporters with and without the minor alleles of SNPs rs10069690, rs2242652 and rs7705526, respectively. The results of comparisons with wild-type *TERTwt* or *TERTth* performed using one-way ANOVA with *post-hoc* Dunnett's tests are shown (\*\*\*)  $P < 0.0001$ , \*\* $P < 0.001$ ). WT, wild type.

between lower enhancer activity and greater telomere length (Fig. 4). Control of telomerase activity is currently poorly understood, and this finding clearly merits further investigation.

SNPs within peak 3 (*TERT* introns 2–4) show strong associations with hormone-related cancers: peak 3 SNP rs10069690 is associated with risk of ER-negative breast cancer<sup>34</sup> and breast cancer in *BRCA1* mutation carriers, consistent with the observation that the majority of breast cancers arising in *BRCA1* mutation carriers are ER negative. This variant has been reported to be associated with prostate cancer<sup>26,54</sup>, and we find it associated with serous invasive ovarian cancer. Although SNPs in peaks 2 and 3 overlap on a physical map, the SNPs most strongly associated with cancer risk or telomere length were not highly correlated with each other ( $r^2$  between rs10069690 and rs7705526 = 0.33; Fig. 2b). This observation suggests that either the associations observed with multiple cancers and SNPs in peak 3 are mediated via a mechanism distinct from control of telomere length or that telomere length in breast, prostate and ovarian cells is under the control of a different set of SNPs from those controlling telomere length in leukocytes. Luciferase reporter assays show that peak 3 contains a silencer of the *TERT* promoter and that the minor allele

of peak 3 SNP rs2242652 further reduces expression. Consistent with this finding, Kote-Jarai *et al.*<sup>54</sup> report that the minor, risk allele of this SNP is associated with reduced *TERT* expression in benign prostate tissue. However, we were unable to identify comparable associations in ovarian or breast tumor tissue, possibly because *TERT* expression is severely dysregulated in most tumors. Taken together, our luciferase assays indicate that either reduced signal from regulatory elements in peaks 1 and 3 or increased signal from peak 2 increases risk of specific cancer types.

It should be noted that the minor allele of rs2242652 is associated with significantly lower risk of prostate cancer<sup>54</sup> (OR = 0.84, 95% CI = 0.81–0.87;  $P_{\text{trend}} = 1 \times 10^{-23}$ ) but with significantly higher risks of breast and ovarian cancers (Tables 1 and 2). Similarly, a nearby SNP, rs401681, is associated with higher risks of cancers of the lung, bladder, testes and cervix and basal cell carcinoma but with lower risk of melanoma<sup>28,30,31</sup>. Such inverted associations might be due to tissue-specific interactions that need further examination.

We have additionally shown that the minor allele of rs10069690 affects splicing and is associated with transcription of a novel truncated isoform resulting from the introduction of a premature stop

codon (Supplementary Fig. 6). We do not yet know whether this isoform affects canonical telomerase activity or how it changes activity. We further identified new open chromatin signatures overlapping rs10069690 in breast stromal and myoepithelial/stem cell fractions but not in progenitor or differentiated luminal epithelial cell fractions. Senescent stromal cells can stimulate malignant transformation of epithelial cells in *in vitro* and *in vivo* models<sup>55,56</sup>, and the mechanisms mediated by these SNPs merit investigation in future studies.

The SNPs originally reported to be associated with risk of lung (rs402710)<sup>57</sup> and breast (rs3816659)<sup>58</sup> cancers (Supplementary Table 10) were not associated with any cancer in this study. Moreover, SNP rs2736100 in peak 2 has been reported to be associated with glioma and lung and testicular cancers<sup>27,28,31,57,59–62</sup>, whereas nearby SNP rs2853677 was reported to be associated with glioma in the Han Chinese population<sup>63</sup>. Despite their physical proximity, these SNPs are not highly correlated with rs7705526 ( $r^2 = 0.52$  and  $0.18$ , respectively), nor do they show independent associations with telomere length after adjustment for rs7705526. Thus, variants underlying susceptibility to different cancer types are different from the set of variants in the *TERT* region mediating changes in telomere length.

One limitation of this study is the incomplete representation of all SNPs at 5p15.33 on the iCOGS chip, which was designed in March 2010 using SNPs catalogued in HapMap 3 together with those from the pilot study of the 1000 Genomes Project<sup>35</sup>. To help fill known gaps on the iCOGS chip, additional SNPs were genotyped from the October 2010 1000 Genomes Project data release, and imputation was based on the most recent January 2012 release. However, several gaps remain across the *TERT* locus, and the existence of these gaps, coupled with the low linkage disequilibrium across the region (Fig. 2), raises the possibility that there could be more independent associations that we have not yet detected. Furthermore, the incomplete SNP catalog at the time of study design means that we cannot assume with certainty that the true causal variants, directly responsible for the observed association peaks, were captured in our analysis. It is also possible that additional rare variants not specifically investigated in this study could have functional effects within this locus. Further resequencing of this region is needed to uncover the full spectrum of variation and phenotype associations. Another limitation is that telomere length was measured in DNA from leukocytes rather than from breast or ovarian tissue. Whereas we obtained suitable blood DNA for measurements in >53,000 subjects (a necessary sample size for adequate statistical power), obtaining comparable qualities and quantities of DNA from normal breast or ovary cells would be almost impossible. Telomere lengths measured in different tissues within one individual have been shown to be highly correlated<sup>64–66</sup>, meaning that leukocyte telomere lengths are likely to be good surrogates for the corresponding lengths in other tissues. Furthermore, one of our aims was to investigate whether the previously reported associations between mean telomere length and cancer risk might be mediated by *TERT* variants, and such studies have been based on telomere length measured in blood cell DNA. Another limitation was that we were unable to stratify OCAC ovarian cancer cases by *BRCA1* and *BRCA2* mutation status because this information was not available; nor was there sufficient power to evaluate ovarian cancer risk in mutation carriers in CIMBA.

Our findings provide evidence relevant to the hypothesis that shorter telomeres increase cancer risks: associations in the *TERT* promoter (peak 1) fit this hypothesis best, whereas those in peaks 2 and 3 (*TERT* introns 2–4) and other reported 5p15.33 SNP cancer associations (Supplementary Table 10) do not. Thus, it would seem that the majority of cancer associations within the *TERT* locus

are mediated via alternative mechanisms involving the *TERT* gene. The protein product of *TERT* has functions beyond the telomerase-mediated extension of telomeres<sup>67</sup>. These non-canonical functions of *TERT* strongly resemble those mediated by *MYC* and *WNT*<sup>68</sup>, which are upstream regulators of proliferation, differentiation and migration. *TERT* also modulates *WNT*/ $\beta$ -catenin signaling<sup>69</sup>, and ectopic *TERT* expression induces increased cell division and decreased apoptosis in primary mammary cells, independent of telomere elongation<sup>70</sup>.

In conclusion, this study provides definitive evidence for genetic control of telomere length by common genetic variants in the *TERT* locus. Additionally, we report multiple, independent *TERT* SNP associations with breast cancer risk, confirming previously reported associations and identifying new associations in both the general population and in *BRCA1* mutation carriers. We also provide, for the first time to our knowledge, highly significant evidence for the association of distinct *TERT* SNPs with serous LMP and invasive ovarian cancer risks. Our results show that the relationships between *TERT* genotype, telomere length and cancer risk are complex and that the *TERT* locus may influence cancer risk through multiple mechanisms.

**URLs.** HapMap 3 catalog, <http://www.sanger.ac.uk/resources/downloads/human/hapmap3.html>; Wellcome Trust Case Control Consortium investigators, <http://www.wtccc.org.uk/>; investigators and institutions constituting the TCGA research network, <http://cancergenome.nih.gov/>.

## METHODS

Methods and any associated references are available in the [online version of the paper](#).

*Note: Supplementary information is available in the online version of the paper.*

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- McEachern, M.J., Krauskopf, A. & Blackburn, E.H. Telomeres and their control. *Annu. Rev. Genet.* **34**, 331–358 (2000).
- Palm, W. & de Lange, T. How shelterin protects mammalian telomeres. *Annu. Rev. Genet.* **42**, 301–334 (2008).
- Baird, D.M. Telomeres. *Exp. Gerontol.* **41**, 1223–1227 (2006).
- Moyzis, R.K. *et al.* A highly conserved repetitive DNA sequence, (TTAGGG)<sub>n</sub>, present at the telomeres of human chromosomes. *Proc. Natl. Acad. Sci. USA* **85**, 6622–6626 (1988).
- Allsopp, R.C. *et al.* Telomere length predicts replicative capacity of human fibroblasts. *Proc. Natl. Acad. Sci. USA* **89**, 10114–10118 (1992).
- Harley, C.B. Telomere loss: mitotic clock or genetic time bomb? *Mutat. Res.* **256**, 271–282 (1991).
- Levy, M.Z. *et al.* Telomere end-replication problem and cell aging. *J. Mol. Biol.* **225**, 951–960 (1992).
- Counter, C.M. *et al.* Telomere shortening associated with chromosome instability is arrested in immortal cells which express telomerase activity. *EMBO J.* **11**, 1921–1929 (1992).
- Hiyama, E. *et al.* Telomerase activity in human breast tumors. *J. Natl. Cancer Inst.* **88**, 116–122 (1996).
- Stampfer, M.R. & Yaswen, P. Human epithelial cell immortalization as a step in carcinogenesis. *Cancer Lett.* **194**, 199–208 (2003).
- Alter, B.P. *et al.* Telomere length is associated with disease severity and declines with age in dyskeratosis congenita. *Haematologica* **97**, 353–359 (2012).
- Njajou, O.T. *et al.* Telomere length is paternally inherited and is associated with parental lifespan. *Proc. Natl. Acad. Sci. USA* **104**, 12135–12139 (2007).
- Slagboom, P.E., Droog, S. & Boomsma, D.I. Genetic determination of telomere size in humans: a twin study of three age groups. *Am. J. Hum. Genet.* **55**, 876–882 (1994).
- Mirabello, L. *et al.* The association of telomere length and genetic variation in telomere biology genes. *Hum. Mutat.* **31**, 1050–1058 (2010).
- Pooley, K.A. *et al.* No association between *TERT-CLPTM1L* single nucleotide polymorphism rs401681 and mean telomere length or cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **19**, 1862–1865 (2010).
- Mocellin, S. *et al.* Telomerase reverse transcriptase locus polymorphisms and cancer risk: a field synopsis and meta-analysis. *J. Natl. Cancer Inst.* **104**, 840–854 (2012).
- Soerensen, M. *et al.* Genetic variation in *TERT* and *TERC* and human leukocyte telomere length and longevity: a cross-sectional and longitudinal analysis. *Aging Cell* **11**, 223–227 (2012).
- McGrath, M. *et al.* Telomere length, cigarette smoking, and bladder cancer risk in men and women. *Cancer Epidemiol. Biomarkers Prev.* **16**, 815–819 (2007).
- Pooley, K.A. *et al.* Telomere length in prospective and retrospective cancer case-control studies. *Cancer Res.* **70**, 3170–3176 (2010).
- Shen, J. *et al.* Telomere length, oxidative damage, antioxidants and breast cancer risk. *Int. J. Cancer* **124**, 1637–1643 (2009).
- Wentzensen, I.M. *et al.* The association of telomere length and cancer: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* **20**, 1238–1250 (2011).
- De Vivo, I. *et al.* A prospective study of relative telomere length and postmenopausal breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **18**, 1152–1156 (2009).
- Zee, R.Y. *et al.* Mean telomere length and risk of incident colorectal carcinoma: a prospective, nested case-control approach. *Cancer Epidemiol. Biomarkers Prev.* **18**, 2280–2282 (2009).
- Baird, D.M. Variation at the *TERT* locus and predisposition for cancer. *Expert Rev. Mol. Med.* **12**, e16 (2010).
- Beesley, J. *et al.* Functional polymorphisms in the *TERT* promoter are associated with risk of serous epithelial ovarian and breast cancers. *PLoS ONE* **6**, e24987 (2011).
- Kote-Jarai, Z. *et al.* Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study. *Nat. Genet.* **43**, 785–791 (2011).
- Landi, M.T. *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.* **85**, 679–691 (2009).
- Rafnar, T. *et al.* Sequence variants at the *TERT-CLPTM1L* locus associate with many cancer types. *Nat. Genet.* **41**, 221–227 (2009).
- Shete, S. *et al.* Genome-wide association study identifies five susceptibility loci for glioma. *Nat. Genet.* **41**, 899–904 (2009).
- Stacey, S.N. *et al.* New common variants affecting susceptibility to basal cell carcinoma. *Nat. Genet.* **41**, 909–914 (2009).
- Turnbull, C. *et al.* Variants near *DMRT1*, *TERT* and *ATF7IP* are associated with testicular germ cell cancer. *Nat. Genet.* **42**, 604–607 (2010).
- Wang, Y. *et al.* Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nat. Genet.* **40**, 1407–1409 (2008).
- Johnatty, S.E. *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.* **6**, e1001016 (2010).
- Haiman, C.A. *et al.* A common variant at the *TERT-CLPTM1L* locus is associated with estrogen receptor-negative breast cancer. *Nat. Genet.* **43**, 1210–1214 (2011).
- 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* **467**, 1061–1073 (2010).
- Michailidou, K. *et al.* Large-scale genotyping identifies 41 new loci associated with breast cancer risk. *Nat. Genet.* published online; doi:10.1038/ng.2563 (27 March 2013).
- Pharoah, P.D.P. *et al.* GWAS meta-analysis and replication identifies three new common susceptibility loci for ovarian cancer. *Nat. Genet.* published online; doi:10.1038/ng.2564 (27 March 2013).
- Garcia-Closas, M. *et al.* Genome-wide association studies identify four ER negative-specific breast cancer risk loci. *Nat. Genet.* published online; doi:10.1038/ng.2561 (27 March 2013).
- Rosenbloom, K.R. *et al.* ENCODE whole-genome data in the UCSC Genome Browser: update 2012. *Nucleic Acids Res.* **40**, D912–D917 (2012).
- Giresi, P.G. *et al.* FAIRE (Formaldehyde-Assisted Isolation of Regulatory Elements) isolates active regulatory elements from human chromatin. *Genome Res.* **17**, 877–885 (2007).
- Taylor, J. *et al.* ESPERR: learning strong and weak signals in genomic sequence alignments to identify functional elements. *Genome Res.* **16**, 1596–1604 (2006).
- Lim, E. *et al.* Aberrant luminal progenitors as the candidate target population for basal tumor development in *BRCA1* mutation carriers. *Nat. Med.* **15**, 907–913 (2009).

43. Chen, Y.J. *et al.* PAX8 regulates telomerase reverse transcriptase and telomerase RNA component in glioma. *Cancer Res.* **68**, 5724–5732 (2008).
44. Colgin, L.M. *et al.* The hTERT $\alpha$  splice variant is a dominant negative inhibitor of telomerase activity. *Neoplasia* **2**, 426–432 (2000).
45. Sæbøe-Larsen, S., Fossberg, E. & Gaudernack, G. Characterization of novel alternative splicing sites in human telomerase reverse transcriptase (*hTERT*): analysis of expression and mutual correlation in mRNA isoforms from normal and tumour tissues. *BMC Mol. Biol.* **7**, 26 (2006).
46. Killian, A. *et al.* Isolation of a candidate human telomerase catalytic subunit gene, which reveals complex splicing patterns in different cell types. *Hum. Mol. Genet.* **6**, 2011–2019 (1997).
47. Wick, M., Zubov, D. & Hagen, G. Genomic organization and promoter characterization of the gene encoding the human telomerase reverse transcriptase (*hTERT*). *Gene* **232**, 97–106 (1999).
48. Desmet, F.O. *et al.* Human Splicing Finder: an online bioinformatics tool to predict splicing signals. *Nucleic Acids Res.* **37**, e67 (2009).
49. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* **474**, 609–615 (2011).
50. Weischer, M. *et al.* Short telomere length, myocardial infarction, ischemic heart disease, and early death. *Arterioscler. Thromb. Vasc. Biol.* **32**, 822–829 (2012).
51. Codd, V. *et al.* Common variants near *TERC* are associated with mean telomere length. *Nat. Genet.* **42**, 197–199 (2010).
52. Levy, D. *et al.* Genome-wide association identifies *OBFC1* as a locus involved in human leukocyte telomere biology. *Proc. Natl. Acad. Sci. USA* **107**, 9293–9298 (2010).
53. Willeit, P. *et al.* Telomere length and risk of incident cancer and cancer mortality. *J. Am. Med. Assoc.* **304**, 69–75 (2010).
54. Kote-Jarai, Z. *et al.* Fine-mapping identifies multiple prostate cancer risk loci on 5p15, one of which associates with *TERT* expression. *Hum. Mol. Genet.* published online; doi:10.1093/hmg/ddt086 (27 March 2013).
55. Krtolica, A. *et al.* Senescent fibroblasts promote epithelial cell growth and tumorigenesis: a link between cancer and aging. *Proc. Natl. Acad. Sci. USA* **98**, 12072–12077 (2001).
56. Lawrenson, K. *et al.* Senescent fibroblasts promote neoplastic transformation of partially transformed ovarian epithelial cells in a three-dimensional model of early stage ovarian cancer. *Neoplasia* **12**, 317–325 (2010).
57. McKay, J.D. *et al.* Lung cancer susceptibility locus at 5p15.33. *Nat. Genet.* **40**, 1404–1406 (2008).
58. Shen, J. *et al.* Multiple genetic variants in telomere pathway genes and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **19**, 219–228 (2010).
59. Hu, 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.* **43**, 792–796 (2011).
60. Mushihiro, T. *et al.* A genome-wide association study identifies an association of a common variant in *TERT* with susceptibility to idiopathic pulmonary fibrosis. *J. Med. Genet.* **45**, 654–656 (2008).
61. Truong, T. *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.* **102**, 959–971 (2010).
62. Zou, P. *et al.* The *TERT* rs2736100 polymorphism and cancer risk: a meta-analysis based on 25 case-control studies. *BMC Cancer* **12**, 7 (2012).
63. Zhao, Y.M. *et al.* Fine-mapping of a region of chromosome 5p15.33 (*TERT-CLPTM1L*) suggests a novel locus in *TERT* and a *CLPTM1L* haplotype are associated with glioma susceptibility in a Chinese population. *Int. J. Cancer* **129**, 2463–2472 (2011).
64. Takubo, K. *et al.* Telomere lengths are characteristic in each human individual. *Exp. Gerontol.* **37**, 523–531 (2002).
65. Gadalla, S.M. *et al.* Telomere length in blood, buccal cells, and fibroblasts from patients with inherited bone marrow failure syndromes. *Aging (Albany NY)* **2**, 867–874 (2010).
66. Thomas, P., O'Callaghan, N.J. & Fenech, M. Telomere length in white blood cells, buccal cells and brain tissue and its variation with ageing and Alzheimer's disease. *Mech. Ageing Dev.* **129**, 183–190 (2008).
67. Greider, C.W. & Blackburn, E.H. Identification of a specific telomere terminal transferase activity in *Tetrahymena* extracts. *Cell* **43**, 405–413 (1985).
68. Choi, J. *et al.* TERT promotes epithelial proliferation through transcriptional control of a Myc- and Wnt-related developmental program. *PLoS Genet.* **4**, e10 (2008).
69. Park, J.I. *et al.* Telomerase modulates Wnt signalling by association with target gene chromatin. *Nature* **460**, 66–72 (2009).
70. Mukherjee, S. *et al.* Separation of telomerase functions by reverse genetics. *Proc. Natl. Acad. Sci. USA* **108**, E1363–E1371 (2011).

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Dansonka-Mieszkowska<sup>189</sup>, Arja Jukkola-Vuorinen<sup>190</sup>, Iwona K Rzepecka<sup>189</sup>, Katri Pylkäs<sup>67,68</sup>, Mariusz Bidzinski<sup>191</sup>, Saila Kauppila<sup>192</sup>, Antoinette Hollestelle<sup>166</sup>, Caroline Seynaeve<sup>166</sup>, Rob A E M Tollenaar<sup>193</sup>, Katarzyna Durda<sup>72</sup>, Katarzyna Jaworska<sup>72,194</sup>, Jaana M Hartikainen<sup>73,74</sup>, Veli-Matti Kosma<sup>73,74</sup>, Vesa Kataja<sup>74</sup>, Natalia N Antonenkova<sup>195</sup>, Jirong Long<sup>78</sup>, Martha Shrubsole<sup>78</sup>, Sandra Deming-Halverson<sup>78</sup>, Artitaya Lophatananon<sup>84,85</sup>, Pornthep Siriwanarangsarn<sup>196</sup>, Sarah Stewart-Brown<sup>84</sup>, Nina Ditsch<sup>197</sup>, Peter Lichtner<sup>198</sup>, Rita K Schmutzler<sup>199,200</sup>, Hidemi Ito<sup>90</sup>, Hiroji Iwata<sup>201</sup>, Kazuo Tajima<sup>90</sup>, Chiu-Chen Tseng<sup>9</sup>, Daniel O Stram<sup>9</sup>, David van den Berg<sup>9</sup>, Cheng Har 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## ONLINE METHODS

**SNP selection and genotyping.** Most SNPs were genotyped on the iCOGS custom array<sup>36,37,71</sup>. SNPs at 5p15.33 (Build 36 positions 1,280,000–1,415,000; Build 37 positions 1,227,693–1,361,969) were selected on the basis of published cancer associations, from the March 2010 release of the 1000 Genomes Project<sup>35</sup>. These included all known SNPs with MAF > 0.02 in Europeans and  $r^2 > 0.1$  with the then-known cancer-associated SNPs (rs402710 (ref. 57) and/or rs3816659 (ref. 58)), plus a tagging set for all known SNPs in the linkage disequilibrium blocks encompassing the genes in the region (*SLC6A18*, *TERT* and *CLPTMIL*). An additional 30 SNPs in *TERT* were selected through a telomere length candidate gene approach. In total, 134 SNPs were selected, 121 of which were successfully manufactured; 110 of those passed quality control<sup>36</sup> in BCAC and CIMBA, and 108 passed quality control in OCAC (**Supplementary Tables 1–3**). After genotyping, these SNPs were complemented with 22 SNPs, selected from the October 2010 release of the 1000 Genomes Project to improve coverage. These were genotyped in two BCAC studies, SEARCH<sup>72</sup> and CCHS<sup>73</sup>, using a Fluidigm array according to the manufacturer's instructions. To improve SNP density further, comprehensive genotype data for the locus were imputed for all subjects on the basis of the January 2012 1000 Genomes Project release. The genotype imputation process is described in refs. 36–38. All participants provided written informed consent. Ethical approval for each study/consortium is described in detail in refs. 36–38.

**Samples and quality control.** Study characteristics, iCOGS methodology and quality control for cancer risk analyses are detailed elsewhere<sup>36–38</sup>. We measured telomere length in 6,766 control samples from the SEARCH study; 1,569 of these were accrued by SEARCH itself<sup>36</sup>, 793 were collected as part of the Sisters in Breast Screening (SIBS) study<sup>15</sup>, and 4,404 were cancer-free participants in the European Prospective Investigation into Cancer (EPIC)-Norfolk study<sup>19</sup>. We also measured telomere length in 8,841 participants in CCHS<sup>73,74</sup> and in 38,145 participants in the Copenhagen General Population Study (CGPS)<sup>75,76</sup>. Genotype clusters were visually inspected for the most strongly associated SNPs (**Supplementary Fig. 2**). For all studies, ancestry was assigned using HapMap (release 22) genotype data for European, African and Asian populations as reference (for BCAC and CIMBA, using multidimensional scaling; for OCAC, using LAMP<sup>77</sup>). All CIMBA analyses were restricted to individuals of European ancestry. For BCAC, separate estimates for individuals of east Asian and African-American ancestry were also derived. For OCAC, limited analyses of non-European ancestry groups were also performed. A subset of BCAC and OCAC cases and controls was used in previous breast and ovarian cancer association studies of individual SNPs<sup>78</sup>. However, the associations with the key SNPs (rs10069690, rs2736108 and rs7705526) remained significant after excluding this subset of cases and controls from analysis, demonstrating similar ORs.

**Telomere length measurement.** Telomere length was measured in SEARCH using a modified version of the protocol described elsewhere<sup>19,79</sup>. Twelve percent of samples were run in duplicate. Failed PCR reactions were not repeated. Telomere length was measured in CCHS and CGPS with a modified version of the protocol described elsewhere<sup>50,80</sup>. Each individual was measured in quadruplicate. After exclusion of outliers, average cycle threshold ( $C_T$ ) values of the remaining samples were calculated. Failed measurements were repeated up to twice. For meta-analysis, telomere length measurements from SEARCH were converted to the same scale as that used for the CCHS and CGPS measurements on the basis of parameters from the linear regression between corresponding 5-percentile groups (including the 5th, 10th, 15th, 20th, 25th, 30th, 35th, 40th, 45th, 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th, 90th, 95th, 97th and 98th percentiles) in each 10-year age group of women from CCHS and SEARCH (**Supplementary Fig. 7**). This measure of telomere length was used for all the analyses and then converted into fold change (RTL) to aid interpretation (**Supplementary Fig. 7**).

**Statistical analyses.** SNP associations with telomere length were evaluated using linear regression to model the fold change in telomere length per minor allele, adjusted for age, 384-well plate, sex, 7 principal components and study. Each SNP was coded as the number of minor alleles (0, 1 or 2 for genotyped SNPs and the inferred genotype for imputed SNPs). The test of association was based on the 1-degree-of-freedom trend test statistic. We also performed separate analyses (SEARCH, CCHS females, CCHS males, CGPS females and

CGPS males) and combined the parameter estimates in a fixed-effect meta-analysis in STATA (StataCorp). Associations with breast and ovarian cancer risks in BCAC and OCAC were evaluated by comparing genotype frequencies in cases and controls using unconditional logistic regression. Analyses were adjusted for study and by seven principal components in BCAC<sup>36</sup> and five principal components in OCAC<sup>37</sup>. Nine OCAC studies with case-only genotype data were paired with case-control studies from similar geographic regions, resulting in 34 analysis study strata. The principal analysis fitted each SNP as an allelic dose and tested for association using a 1-degree-of-freedom trend test, but genotype-specific risks were also obtained. Associations between genotypes and breast cancer risk in CIMBA studies (*BRCA1* mutation carriers) were evaluated using a 1-degree-of-freedom per-allele trend score test, based on modeling the retrospective likelihood of the observed genotypes conditional on breast cancer phenotypes<sup>81</sup>. To allow for non-independence among related individuals, an adjusted version of the score test was used in which the variance of the score was derived, taking into account the correlation between the genotypes by estimating the kinship coefficient for each pair of individuals using the available genotype data<sup>82</sup>. Per-allele HR estimates were obtained by maximizing the retrospective likelihood. All analyses were stratified by country of residence. US and Canadian strata were further stratified on the basis of reported Ashkenazi Jewish ancestry.

Conditional analyses were performed to identify SNPs independently associated with each phenotype. To identify the most parsimonious model, all SNPs with marginal  $P$  value < 0.001 were included in forward selection regression analyses with a threshold for inclusion of  $P < 1 \times 10^{-4}$  and with terms for age (for telomere length only), principal components and study. Similarly, forward selection Cox regression analysis was performed for *BRCA1* mutation carriers, stratified by country of residence, using the same  $P$ -value thresholds. This approach provides valid association tests, although the estimates can be biased<sup>81,83</sup>. Parameter estimates for the most parsimonious model were obtained using the retrospective likelihood approach.

**FACS.** Normal breast tissue was donated by women undergoing reduction mammoplasty surgery. These individuals provided written consent, and all work was performed with full local institutional human ethics approval. Tissue was dissociated as described previously<sup>84</sup>. Cells were prepared for flow cytometry as described previously<sup>42</sup> by staining with a cocktail of Lin<sup>+</sup> markers (CD31-PE, CD45-PE and CD235a-PE), EpCAM-FITC, CD49f-PE-Cy5 and Sytox Blue. Cells were then processed by a BD FACSAria II Cell Sorter, and live cells negative for immunostaining of Lin<sup>+</sup> markers were sorted into four subpopulations on the basis of their EpCAM-FITC and CD49f-PE-Cy5 fluorescence.

**FAIRE analysis.** Cell pellets derived from FACS fractionation of breast tissue samples were cross-linked in 1% formaldehyde and lysed in 200  $\mu$ l of Tris-buffered 1% SDS lysis buffer containing protease inhibitors. Lysates were sonicated using a QSONICA Model Q125 Ultra Sonic Processor to shear chromatin to fragments of 200 bp to 1 kb in length. Insoluble cell material was removed through centrifugation, and supernatants were equally divided into 100- $\mu$ l input and FAIRE samples. Input samples were incubated overnight at 65 °C to reverse cross-linking. All samples were purified through two rounds of phenol-chloroform extraction, and DNA was recovered through ethanol precipitation and resuspended in water for use as PCR template. Sequences for PCR primers are listed in **Supplementary Table 11**.

**Plasmid construction and luciferase assays.** *TERT* promoter variants were introduced into pGL3-*TERT*-3915 (ref. 43) by site-directed mutagenesis (Agilent Technologies). *TERT* PRE-A (hg19; chr. 5: 1,284,900–1,287,087) and PRE-B (chr. 5: 1,279,401–1,282,763) were PCR amplified using KAPAHiFi DNA polymerase (Geneworks) and cloned into pGL3-*TERT*-3915 or the vector encoding the minor alleles of rs2736107, rs2736108 and rs2736107. Individual SNPs were incorporated using overlap extension PCR. Sequences for PCR primers are listed in **Supplementary Table 11**. Cells were transfected with equimolar amounts of luciferase reporter plasmids and 50 ng of pRLTK using siPORT NeoFX Transfection Agent (Ambion), according to the manufacturer's instructions, and harvested after 48 h. Luminescence activity was measured with a Wallac Victor3 1420 multilabel counter, and data from three replicates per construct were analyzed by one-way ANOVA with post-hoc Dunnett's tests.

**Mini-gene construction and quantitative RT-PCR analysis.** *TERT* intron 4 was synthesized by GenScript and subcloned into pIRES-*TERT*<sup>44</sup>. The minor alleles at rs10069690 and rs2242652 were introduced by site-directed mutagenesis (Agilent Technologies). The resultant plasmids, designated pIRES-*TERT*int4-WT (wild-type intron 4), pIRES-*TERT*int4-rs10069690, pIRES-*TERT*int4-rs2242652 and pIRES-*TERT*int4-DM (minor alleles at both sites), were transfected into cells using siPORT NeoFX Transfection Agent, and cells were harvested after 24 h. Total RNA was extracted using the RNeasy Mini kit (Qiagen) and digested with DNase I (Invitrogen). cDNA was synthesized from 1 µg of RNA by random priming using SuperScript III reverse transcriptase (Invitrogen). Samples were screened for the presence of *TERT* splice variants by RT-PCR. Sequences for PCR primers are listed in **Supplementary Table 11**.

**Molecular correlations at the 5p15.33 locus.** For each gene within 1 Mb of the *TERT* locus, we performed the following assays: (i) gene expression analysis in ovarian cancer cell lines ( $n = 50$ ) compared to ovarian surface epithelial and fallopian tube secretory cell lines ( $n = 73$ ) and tissues from high-grade serous ovarian cancers; (ii) methylation analysis in high-grade serous ovarian cancers compared to normal tissues and methylation quantitative trait locus (mQTL) analysis; and (iii) expression quantitative trait locus (eQTL) analysis to evaluate genotype–gene expression associations in normal high-grade serous ovarian cancer precursor tissues. We also evaluated these genes *in silico* in the somatic data from TCGA<sup>49</sup>. We profiled the spectrum of noncoding regulatory elements in ovarian surface epithelial and fallopian tube secretory cell lines using a combination of FAIRE sequencing (FAIRE-seq<sup>40</sup>) and RNA sequencing (RNA-seq).

71. Gaudet, M.M. *et al.* Identification of a *BRCA2*-specific modifier locus at 6p24 related to breast cancer risk. *PLoS Genet.* **9**, e1003173 (2013).
72. Azzato, E.M. *et al.* Association between a germline *OCA2* polymorphism at chromosome 15q13.1 and estrogen receptor–negative breast cancer survival. *J. Natl. Cancer Inst.* **102**, 650–662 (2010).
73. Bojesen, S.E., Tybjaerg-Hansen, A. & Nordestgaard, B.G. Integrin β3 Leu33Pro homozygosity and risk of cancer. *J. Natl. Cancer Inst.* **95**, 1150–1157 (2003).
74. Allin, K.H., Bojesen, S.E. & Nordestgaard, B.G. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. *J. Clin. Oncol.* **27**, 2217–2224 (2009).
75. Allin, K.H. *et al.* C-reactive protein and the risk of cancer: a mendelian randomization study. *J. Natl. Cancer Inst.* **102**, 202–206 (2010).
76. Zacho, J. *et al.* Genetically elevated C-reactive protein and ischemic vascular disease. *N. Engl. J. Med.* **359**, 1897–1908 (2008).
77. Sankararaman, S. *et al.* Estimating local ancestry in admixed populations. *Am. J. Hum. Genet.* **82**, 290–303 (2008).
78. Terry, K.L. *et al.* Telomere length and genetic variation in telomere maintenance genes in relation to ovarian cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **21**, 504–512 (2012).
79. Cawthon, R.M. Telomere measurement by quantitative PCR. *Nucleic Acids Res.* **30**, e47 (2002).
80. Cawthon, R.M. Telomere length measurement by a novel monochrome multiplex quantitative PCR method. *Nucleic Acids Res.* **37**, e21 (2009).
81. Barnes, D.R. *et al.* Evaluation of association methods for analysing modifiers of disease risk in carriers of high-risk mutations. *Genet. Epidemiol.* **36**, 274–291 (2012).
82. Antoniou, A.C. *et al.* A locus on 19p13 modifies risk of breast cancer in *BRCA1* mutation carriers and is associated with hormone receptor–negative breast cancer in the general population. *Nat. Genet.* **42**, 885–892 (2010).
83. Antoniou, A.C. *et al.* A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. *Genet. Epidemiol.* **29**, 1–11 (2005).
84. Eirew, P. *et al.* A method for quantifying normal human mammary epithelial stem cells with *in vivo* regenerative ability. *Nat. Med.* **14**, 1384–1389 (2008).