Published in final edited form as:
Mol Carcinog. 2013 July ; 52(7): 507–513. doi:10.1002/mc.21885.

TERT's role in colorectal carcinogenesis

Andrew J. Pellatt[1], **Roger K. Wolff**[1], **Jennifer Herrick**[1], **Abbie Lundgreen**[1], and **Martha L. Slattery**[1]

[1]Department of Internal Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah, USA

Abstract

Telomerase reverse transcriptase (TERT) is one of the main functional subunits of the telomerase enzyme, which functions to increase telomere length. Studies have suggested that *TERT* may be important to the etiology of colorectal cancer. In this study we evaluate seven *TERT* SNPs in 1555 incident colon cancer cases and 1956 matched controls and in 754 incident rectal cancer cases and 959 matched controls. We observed that two *TERT* SNPs were associated with colon cancer. *TERT* rs2736118 was associated with increased risk of colon cancer (OR =1.31, 95% CI 1.02,1.69) and *TERT-CLPTM1L* rs2853668 was inversely associated with colon cancer (OR = 0.71, 95% CI 0.55,0.92). *TERT-CLPTM1L* rs2853668 also was inversely associated with rectal cancer (OR 0.62 95% CI 0.43,0.90). BMI interacted significantly with three *TERT* SNPs to alter risk of colon cancer. Those with the variant allele and who were obese had the greatest risk of colon cancer. *TERT-CLPTM1L* rs2853668 interacted significantly with aspirin/NSAID use, where those with the AA genotype had a much lower risk of colon cancer when using aspirin/NSAIDs than those with the other genotypes. Several *TERT* SNPs were uniquely associated with CIMP+ and MSI tumors. These data confirm earlier reports of the association between *TERT-CLPTM1L* and colon and rectal cancer. Our detection of a significant interaction with BMI for multiple *TERT* SNPs and unique associations with CIMP+ tumors enhance our understanding of *TERT's* role in colon carcinogenesis.

Keywords

Colon Cancer; Rectal Cancer; TERT; CIMP+; BMI

Introduction

Colorectal cancer is among the most common types of cancer, with an estimated one million newly diagnosed cases per year [1]. Recent studies have examined the role played by telomeres and the telomerase enzyme in carcinogenesis, including colorectal carcinogenesis [1–4]. Telomeres are located on the ends of chromosomes and help protect genomic integrity and stability [5]. They achieve this by preventing chromosomal shortening and the loss of genetic material, and preventing chromosomal rearrangements. A recent genome-wide association study (GWAS) found that the single nucleotide polymorphism (SNP) rs2853668 was significantly associated with colorectal cancer risk [6]. This SNP is 5.1KB upstream of telomerase reverse transcriptase (*TERT*) which is a catalytic subunit of the telomerase enzyme.

Corresponding author: Martha L. Slattery, Ph.D., Department of Internal Medicine, University of Utah Health Sciences Center, 295 Chipeta Way, Salt Lake City, Utah 84108, Phone 801-585-6955, Fax 801-581-3623, marty.slattery@hsc.utah.edu.

The authors have no conflict of interest to report.

TERT is one of the main functional subunits of the telomerase enzyme, which functions to increase telomere length. TERT uses the telomeric RNA subunit of telomerase as a template for the synthesis of single stranded DNA within the telomere, thereby producing $(TTAGGG)_n$ tandem nucleotide repeats. Through the functions of its two subunits, telomerase maintains telomere length as a cell undergoes division. However, most differentiated cells lack telomerase activity so that telomeres shorten with aging. Research has suggested that telomerase activity, and therefore TERT activity, could be present in cancer cells preventing them from undergoing senescence [7, 8].

In this study we examine seven *TERT* SNPs, including *TERT-CLPTM1L* rs2853668, in a large case-control study of colon and rectal cancer. SNPs were selected to capture the genetic variability across the *TERT* gene. We evaluate tumor molecular phenotype to determine if *TERT* is associated with specific colorectal cancer tumor mutations and epigenetic changes. This builds upon earlier reports of a link between carcinogenesis and genomic instability and the accumulation of genetic errors [9]. We hypothesize that tumor molecular phenotype associated with genomic instability or epigenetic changes, such as MSI or CIMP, are more likely associated with *TERT* polymorphisms. We also evaluate if *TERT* interacts with lifestyle factors such as aspirin/NSAID use, cigarette smoking, and body mass index (BMI) to alter cancer risk. These lifestyle factors were evaluated because of their association with colon and rectal cancer as well as their association with telomere length (TL) (unpublished data). Given these factors were associated with TL, it is possible that they modify associations between genetic factors that may influence TL.

Methods

The study population comes from the Diet, Activity, and Lifestyle Study of colorectal cancer. Two populations were used for this study. The first, a population-based incident case-control study of colon cancer with cases (n=1,555) and controls (n=1,956) identified between October 1, 1991 and September 30, 1994. The sample population was composed of individuals living in the Kaiser Permanente Medical Care Program of Northern California (KPMCD), a seven-county area of Utah, and the Twin Cities Metropolitan Area [10]. The second was a population-based incident case-control study of rectal cancer with cases (n=754) and controls (n=959) identified between May 1997 and May 2001. The sample population was composed of individuals from the KPMCD and the state of Utah. To be included in the study, cases had to be between 30 and 79 years of age at the time of diagnosis, English speaking, and competent to give informed consent. Additionally, eligible cases must have no previous history of colorectal cancer, ulcerative colitis, Crohn's disease, or familial adenomatous polyposis. Controls were matched to cases by sex and 5-year age groups [11].

Data collection

Data were collected by trained and certified interviewers using laptop computers [12]. Detailed information was collected on diet, physical activity, medical history, cigarette smoking history, regular use of aspirin/NSAIDs, and body size [13].

Genetic Analysis

Six tagSNPs for *TERT* were selected using the following parameters: LD blocks were defined using a Caucasian LD map and an r^2=0.8; minor allele frequency (MAF) >0.1; range= −1500 bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. TagSNPs were genotyped using a multiplexed bead-array assay format based on GoldenGate chemistry (Illumina, San Diego, California)[14]. A genotyping call rate of 99.85% was attained. Blinded internal replicates represented 4.4% of the sample set; the

duplicate concordance rate was 100%. *TERT-CLPTM1L* rs2853668 was run using a taqMan assay. We have previously evaluated tumors for CpG island methylator phenotype (CIMP), microsatellite instability (MSI), *TP53* mutations, and *KRAS2* mutations [15–18]. Details of methods used to evaluate epigenetic and genetic changes have been described [15–18]. Given the rarity of MSI+ rectal tumors [19] we were unable to evaluate that small subset of tumors.

Statistical Methods

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). We report odds ratios (ORs) and 95% confidence intervals (95%CIs) assessed from adjusted multiple logistic regression models adjusting for age, center, race/ethnicity (approximately 90% Caucasian, 5% African American and 5% Hispanic), and sex which were matching variables for the original study. Inheritance models were selected based on initial review of results from the additive model. When risk estimates indicated that a recessive or dominant model was more appropriate that model was used. We present Wald p values of association for SNPs with colorectal cancer and a p value for linear trend with the additive model are shown. Adjusted multiple-comparison p values (pACT), taking into account tagSNPs within the gene, were estimated using the methods by Conneely and Boehnke [20] via R version 2.11.0 (R Foundation for Statistical Computing, Vienna, Austria using the Wald p value. Lifestyle variables were selected because of their biological plausibility and included factors associated with inflammation and oxidative stress (i.e. recent aspirin or NSAID use) and cigarette smoking (recent or not recent smoker), or BMI. Aspirin/NSAID use and cigarette smoking were categorized into two levels to maximize power. *P* values for interaction were determined using a likelihood-ratio test comparing a full model that included an interaction term with a reduced model without an interaction term.

Results

The study population was mainly non-Hispanic white, male, and over 60 years of age (Table 1). All SNPs except rs2853668 were in Hardy Weinberg Equilibrium (HWE) among controls. SNP rs2853668 was in HWE among cases. Of the seven SNPs evaluated in this study, *TERT* rs2736118 was associated with colon cancer and rs2853668 were associated with colon and rectal cancer (Table 2). *TERT* rs2736118 showed a significant unadjusted association with colon cancer (p=0.048; multiple comparison adjusted p value 0.07). *TERT-CLPTM1L* rs2853668 was inversely associated with both colon cancer (OR 0.71 95% CI 0.55, 0.92) and rectal cancer (OR 0.62 95% CI 0.43, 0.90) with similar magnitudes of association.

In addition to evaluating associations between *TERT* SNPs and overall risk for colon and rectal cancer we evaluated associations between these SNPs and risk for specific tumor molecular phenotypes (data not shown in table). Individuals with a CT or TT genotype for *TERT* rs2242652 were at significantly higher risk of developing a CIMP+ colon tumor (OR for CT/TT vs. CC=1.33 95% Cl 1.05,1.68); individuals who are GG for *TERT* rs2736118 were more likely to develop an MSI colon tumor (OR for GG vs. AA=1.64 95% Cl 1.05, 2.58). Individuals with the GG genotype of *TERT* rs2736100 were at significantly lower risk of developing a CIMP+ rectal tumor (OR for GG vs. TT = 0.30 95% Cl 0.12, 0.72).

Three *TERT* SNPs show a significant interaction with BMI to influence risk of colon cancer (Table 3). *TERT* rs10069690 (p=0.0013), *TERT* rs2242652 (p=0.0119), and *TERT* rs4246742 (p=0.0179) interacted with BMI to influence risk of colon but not rectal cancer. For three of these SNPs, rs10069690 and rs2242652 those who were obese (BMI>30) had a greater risk of colon cancer in the presence of the variant allele. For rs2853668, recent

aspirin/NSAID use had its greatest protective effect among those with the AA genotype. No significant interactions were observed between any of our other six *TERT* SNPs and aspirin/NSAIDs or cigarette smoking. Likewise, we observed no meaningful significant interactions between *TERT* SNPs and rectal cancer.

Discussion

The TERT protein functions within the telomerase enzyme to maintain TL. Therefore, if *TERT* polymorphisms cause missense mutations that alter protein function, TL can be affected and the SNPs can influence cancer risk. Our findings that *TERT* polymorphisms alter risk of colon cancer risk, but not rectal cancer, parallels those observed for TL and colorectal cancer. Shorter TL has been associated with increased risk of colon cancer but not rectal cancer (unpublished data). We observed that *TERT* rs2736118 was associated a 30% increased risk of developing colon cancer and that *TERT-CLPTM1L* rs2853668 was inversely associated with both colon and rectal cancer. Our data suggest that genetic variation in *TERT* was more likely to result in a CIMP+ or MSI colon tumors. Assessment of interaction with lifestyle factors showed that three of the six *TERT* SNPs evaluated interacted significantly with BMI to alter risk of colon cancer, while *TERT-CLPTM1L* rs2853668 interacted with aspirin/NSAID use to alter colon cancer risk.

Other studies have evaluated *TERT* SNPs and risk of colorectal cancer. A recent GWAS study found that rs2853668 showed a significant association with risk of colorectal cancer [7]. That study suggested that the *TERT-CLPTM1L* is a general cancer susceptibility locus with a critical impact on cancer development. This study replicates the earlier finding that this locus is associated with both colon and rectal cancer carcinogenesis. Another study evaluated the association between *TERT-CLPTM1L* rs401681 and various forms of cancer: including breast cancer, colorectal cancer, and melanoma [21]. That study by Pooley and colleagues found no association between that particular SNP and either colorectal cancer risk or TL, and concluded that any association with this SNP and cancer was not mediated through TL. Our data support an association between *TERT-CLPTM1L* rs2853668 and both colon and rectal cancer. However, the mechanism may not be through TL since we observed that this SNP was not associated with TL (unpublished data),

We evaluated the association between interactions of lifestyle factors associated with TL and genetic variation in TERT. We show that *TERT* polymorphisms interacted with BMI and NSAIDs to alter risk of colon cancer; this has not been examined in earlier studies. We observed that multiple *TERT* polymorphisms interacted with BMI to alter risk of colon cancer but not rectal cancer, adding somewhat to the likelihood of a non-spurious association. BMI has been shown to increase risk of colon, but not rectal cancer [22]. A large BMI has been linked to increased levels of insulin and inflammation [23, 24] which are considered elements in pathways of importance to colon carcinogenesis. Likewise, shorter TL has been associated with higher levels of insulin and inflammation [25] as well as with larger BMIs [26]. Our data suggest that having the variant *TERT* genotypes in combination with a large BMI increases risk of colon cancer. While the mechanism may involve both insulin and inflammation, our data imply that when both *TERT* genotypes and obesity are present, the combination of the two have a greater impact than either independently. This may imply that among obese individuals with variant genotypes, TL is shorter than when each situation exists alone.

We also observed that the association between *TERT-CLPTM1L* rs2853668 and colon cancer is modified by use of aspirin/NSAIDs, where the greatest protection is observed from the combination of recent aspirin/NSAID use and having the homozygote variant genotype. This suggests a possible inflammation-related mechanism for this SNP given the reduced

risk associated with aspirin/NSAIDs and colon cancer is thought to stem from reduced inflammation in the gut. Statin therapy has been associated with longer TL with the proposed mechanism being that statins reduce inflammation and the associated oxidative stress [27]. Furthermore, telomere dysfunction has been shown to cause sustained inflammation [28] and shorter telomeres have been associated with pro-inflammatory activity [29, 30]. While the functionality of *TERT-CLPTM1L* rs2853668 is not fully understood, the stronger inverse association with the homozygote variant genotype among aspirin/NSAID users may be from reduced inflammation given what we know about telomeres and inflammation.

It has been suggested by others that *TERT* may influence tumor molecular phenotype [31, 32]. Rampazzo and colleagues observed that shorter TL was associated with MSI tumors although not with *TP53*-mutated tumors. They concluded that erosion of telomeres could lead to genetic instability, which is a mechanism in the neoplastic process. Rampazzo and others also have shown that TL shortening is more common for proximal versus rectal tumors [31, 33]. Both MSI and CIMP+ tumors are more common for colon tumors, especially proximal colon cancer tumors [19]. Our findings in a large sample of both colon and rectal cancers support those previously reported. We add to the earlier findings by demonstrating that *TERT* polymorphisms which could regulate TL length also are associated with MSI+ tumors. We further show that CIMP+ tumors are associated with these polymorphisms, suggesting that erosion of telomeres leading to genetic instability may also be associated with epigenetic changes in tumors.

There are several limitations to the study. First we limited our analysis to only seven *TERT* SNPs and other SNPs in *TERT* may be important. Furthermore, we do not include other genes that have been shown to be related to TL in these analyses. *TERT-CLPTM1L* rs2853668 was not in HWE among controls, although it was in HWE among cases. Genotyping analyses were completed with case and control samples intermixed. Also, a small subset of our data were included in the GWAS and showed virtually identical genotyping results, suggesting that lack of HWE is not from genotyping error. A strength of our study is our extensive data which enables us to evaluate interaction with key lifestyle variables as well as to assess associations with specific tumor molecular phenotype.

In summary, our data support an association between *TERT* polymorphisms and risk of colon cancer. We add to the previous reports by showing that several associations are modified by body size. Additionally, we validate the association of TERT-*CLPTM1L* rs2853668 which was previously associated with colorectal cancer and show that this SNP interacts significant with aspirin/NSAID use to modify colon cancer risk. Assessment of tumor molecular phenotype suggests that *TERT* may operate through CIMP+ and MSI+ pathways.

Acknowledgments

This study was funded by NCI grant CA48998. This research also was supported by the Utah Cancer Registry, which is funded by Contract #N01-PC-67000 from the National Cancer Institute, with additional support from the State of Utah Department of Health, the Northern California Cancer Registry, and the Sacramento Tumor Registry. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official view of the National Cancer Institute. We would like to acknowledge the contributions of Dr. Bette Caan, Donna Schaffer, and Judy Morse at the Kaiser Permanente Medical Care Program in Oakland, California; Sandra Edwards, Roger Edwards, and Leslie Palmer at the University of Utah; and Drs. Kristin Anderson and John Potter at the University of Minnesota for their work on data collection.

References

1. Soreide K, Gudlaugsson E, Skaland I, et al. Metachronous cancer development in patients with sporadic colorectal adenomas-multivariate risk model with independent and combined value of hTERT and survivin. Int J Colorectal Dis. 2008; 23(4):389–400. [PubMed: 18189140]
2. Simsek BC, Pehlivan S, Karaoglu A. Human telomerase reverse transcriptase expression in colorectal tumors: correlations with immunohistochemical expression and clinicopathologic features. Ann Diagn Pathol. 2010; 14(6):413–417. [PubMed: 21074689]
3. Svec J, Ergang P, Mandys V, Kment M, Pacha J. Expression profiles of proliferative and antiapoptotic genes in sporadic and colitis-related mouse colon cancer models. Int J Exp Pathol. 2010; 91(1):44–53. [PubMed: 20096072]
4. Zinn RL, Pruitt K, Eguchi S, Baylin SB, Herman JG. hTERT is expressed in cancer cell lines despite promoter DNA methylation by preservation of unmethylated DNA and active chromatin around the transcription start site. Cancer Res. 2007; 67(1):194–201. [PubMed: 17210699]
5. Mirabello L, Yu K, Kraft P, et al. The association of telomere length and genetic variation in telomere biology genes. Hum Mutat. 2010; 31(9):1050–1058. [PubMed: 20597107]
6. Peters U, Hutter CM, Hsu L, et al. Meta-analysis of new genome-wide association studies of colorectal cancer risk. Hum Genet. 2011
7. Jones AM, Beggs AD, Carvajal-Carmona L, et al. TERC polymorphisms are associated both with susceptibility to colorectal cancer and with longer telomeres. Gut. 2011
8. Bautista CV, Felis CP, Espinet JM, Garcia JB, Salas JV. Telomerase activity is a prognostic factor for recurrence and survival in rectal cancer. Dis Colon Rectum. 2007; 50(5):611–620. [PubMed: 17297554]
9. Watson AJ, Collins PD. Colon cancer: a civilization disorder. Dig Dis. 2011; 29(2):222–228. [PubMed: 21734388]
10. Slattery ML, Potter J, Caan B, et al. Energy balance and colon cancer--beyond physical activity. Cancer Res. 1997; 57(1):75–80. [PubMed: 8988044]
11. Slattery ML, Edwards S, Curtin K, et al. Physical activity and colorectal cancer. Am J Epidemiol. 2003; 158(3):214–224. [PubMed: 12882943]
12. Edwards S, Slattery ML, Mori M, et al. Am J Epidemiol. 1994; 140(11):1020–1028. [PubMed: 7985650]
13. Slattery ML, Jacobs DR Jr. Assessment of ability to recall physical activity of several years ago. Ann Epidemiol. 1995; 5(4):292–296. [PubMed: 8520711]
14. Slattery ML, Herrick JS, Lundgreen A, Fitzpatrick FA, Curtin K, Wolff RK. Genetic variation in a metabolic signaling pathway and colon and rectal cancer risk: mTOR, PTEN, STK11, RPKAA1, PRKAG2, TSC1, TSC2, PI3K and Akt1. Carcinogenesis. 2010; 31(9):1604–1611. [PubMed: 20622004]
15. Samowitz WS, Curtin K, Ma KN, et al. Prognostic significance of p53 mutations in colon cancer at the population level. Int J Cancer. 2002; 99(4):597–602. [PubMed: 11992552]
16. Slattery ML, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. J Natl Cancer Inst. 2000; 92(22):1831–1836. [PubMed: 11078760]
17. Samowitz WS, Curtin K, Schaffer D, Robertson M, Leppert M, Slattery ML. Relationship of Ki-ras mutations in colon cancers to tumor location, stage, and survival: a population-based study. Cancer Epidemiol Biomarkers Prev. 2000; 9(11):1193–1197. [PubMed: 11097226]
18. Slattery ML, Curtin K, Sweeney C, et al. Diet and lifestyle factor associations with CpG island methylator phenotype and BRAF mutations in colon cancer. Int J Cancer. 2007; 120(3):656–663. [PubMed: 17096326]
19. Slattery ML, Curtin K, Wolff RK, et al. A comparison of colon and rectal somatic DNA alterations. Dis Colon Rectum. 2009; 52(7):1304–1311. [PubMed: 19571709]
20. Conneely KN, Boehnke M. So Many Correlated Tests, So Little Time! Rapid Adjustment of P Values for Multiple Correlated Tests. Am J Hum Genet. 2007; 81(6):1158–1168. [PubMed: 17966093]

21. Pooley KA, Tyrer J, Shah M, et al. No association between TERT-CLPTM1L single nucleotide polymorphism rs401681 and mean telomere length or cancer risk. Cancer Epidemiol Biomarkers Prev. 2010; 19(7):1862–1865. [PubMed: 20570912]
22. Slattery ML, Murtaugh M, Caan B, Ma KN, Wolff R, Samowitz W. Associations between BMI, energy intake, energy expenditure, VDR genotype and colon and rectal cancers (United States). Cancer Causes Control. 2004; 15(9):863–872. [PubMed: 15577288]
23. Sastry PS, Parikh P. The earlier age of onset of malignancy in developing world is related to overall infection burden and could be due to the effect on telomere length. Med Hypotheses. 2003; 60(4):573–574. [PubMed: 12615525]
24. Al-Attas OS, Al-Daghri N, Bamakhramah A, Shaun Sabico S, McTernan P, Huang TT. Telomere length in relation to insulin resistance, inflammation and obesity among Arab youth. Acta Paediatr. 2010; 99(6):896–899. [PubMed: 20178511]
25. Al-Attas OS, Al-Daghri NM, Alokail MS, et al. Adiposity and insulin resistance correlate with telomere length in middle-aged Arabs: the influence of circulating adiponectin. Eur J Endocrinol. 2010; 163(4):601–607. [PubMed: 20679357]
26. Njajou OT, Cawthon RM, Blackburn EH, et al. Shorter telomeres are associated with obesity and weight gain in the elderly. Int J Obes (Lond). 2011
27. Saliques S, Teyssier JR, Vergely C, et al. Circulating leukocyte telomere length and oxidative stress: A new target for statin therapy. Atherosclerosis. 2011; 219(2):753–760. [PubMed: 21962402]
28. Amsellem V, Gary-Bobo G, Marcos E, et al. Telomere Dysfunction Causes Sustained Inflammation in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2011
29. Calvert PA, Liew TV, Gorenne I, et al. Leukocyte telomere length is associated with high-risk plaques on virtual histology intravascular ultrasound and increased proinflammatory activity. Arterioscler Thromb Vasc Biol. 2011; 31(9):2157–2164. [PubMed: 21680897]
30. O'Donovan A, Pantell MS, Puterman E, et al. Cumulative inflammatory load is associated with short leukocyte telomere length in the Health, Aging and Body Composition Study. PloS one. 2011; 6(5):e19687. [PubMed: 21602933]
31. Rampazzo E, Bertorelle R, Serra L, et al. Relationship between telomere shortening, genetic instability, and site of tumour origin in colorectal cancers. Br J Cancer. 2010; 102(8):1300–1305. [PubMed: 20386541]
32. Takagi S, Kinouchi Y, Hiwatashi N, et al. Relationship between microsatellite instability and telomere shortening in colorectal cancer. Dis Colon Rectum. 2000; 43(10 Suppl):S12–17. [PubMed: 11052472]
33. Takagi S, Kinouchi Y, Hiwatashi N, et al. Telomere shortening and the clinicopathologic characteristics of human colorectal carcinomas. Cancer. 1999; 86(8):1431–1436. [PubMed: 10526269]

Table 1

Description of study population

		Colon		Rectal	
		Control	**Case**	**Control**	**Case**
		n (%)	**n (%)**	**n (%)**	**n (%)**
Age	30–39	40 (2.04)	23 (1.48)	21 (2.19)	19 (2.52)
	40–49	128 (6.54)	102 (6.56)	101 (10.53)	96 (12.73)
	50–59	326 (16.67)	290 (18.65)	243 (25.34)	196 (25.99)
	60–69	673 (34.41)	538 (34.60)	329 (34.31)	250 (33.16)
	70–79	789 (40.34)	602 (38.71)	265 (27.63)	193 (25.60)
Center	Utah	378 (19.33)	249 (16.01)	365 (38.06)	274 (36.34)
	KPMCP	787 (40.24)	744 (47.85)	594 (61.94)	480 (63.66)
	Minnesota	791 (40.44)	562 (36.14)	0 (0)	0 (0)
Race/Ethnicity	NHW	1828 (93.46)	1428 (91.83)	824 (85.92)	625 (82.89)
	Hispanics	75 (3.83)	59 (3.79)	63 (6.57)	61 (8.09)
	Black	53 (2.71)	68 (4.37)	43 (4.48)	29 (3.85)
	Asian	0	0	29 (3.02)	39 (5.17)
Sex	Male	1047 (53.53)	870 (55.95)	541 (56.41)	451 (59.81)
	Female	909 (46.47)	685 (44.05)	418 (43.59)	303 (40.19)
	Location	SNP	MAF[1]	HWE[2]	
TERT	5p15.33	rs2736118	0.27	0.27	
		rs4246742	0.15	0.15	
		rs10069690	0.25	0.25	
		rs2242652	0.19	0.19	
		rs2736100	0.5	0.5	
		rs2853676	0.26	0.26	
TERT-CLPTM1L		rs2853668	0.26	<0.01	

[1]Minor Allele Frequency (MAF) in control population

[2]Hardy Weinberg Equilibrium (HWE)

Table 2

Associations between *TERT* genotypes and colon and rectal cancer

	Colon						Rectal					
	Controls	Cases					Controls	Cases				
	N	N	OR[1]	(95% CI)	Wald *P*	Trend *P*	N	N	OR	(95% CI)	Wald *P*	Trend *P*
TERT (rs10069690)												
CC	1031	791	1		0.54	0.34	533	419	1		0.47	0.71
CT	760	634	1.08	(0.94, 1.25)			357	269	0.95	(0.77, 1.16)		
TT	137	115	1.06	(0.81, 1.38)			65	62	1.21	(0.83, 1.75)		
TERT (rs2242652)												
CC	1265	972	1		0.13		643	508	1		0.96	
CT/TT	669	566	1.12	(0.97, 1.28)			305	239	0.99	(0.81, 1.22)		
TERT (rs2736100)												
TT	493	410	1		0.06	0.07	270	214	1		0.74	0.64
TG	956	798	1.02	(0.86, 1.20)			465	356	0.97	(0.78, 1.22)		
GG	507	347	0.83	(0.69, 1.01)			224	184	1.07	(0.82, 1.40)		
TERT (rs2736118)												
AA	1040	787	1		0.1	0.05	479	412	1		0. 17	0. 08
AG	769	621	1.07	(0.93, 1.23)			393	279	0.83	(0.68, 1.02)		
GG	143	145	1.31	(1.02, 1.69)			80	57	0.82	(0.57, 1.18)		
TERT (rs2853676)												
GG	1059	825	1		0.70	0.71	556	407	1		0.13	0.21
GA	752	621	1.06	(0.92, 1.22)			330	295	1.23	(1.00, 1.51)		
AA	145	109	0.98	(0.75, 1.28)			72	51	1.01	(0.69, 1.48)		
TERT (rs4246742)												
AA	1375	1095	1		0.76		687	506	1		0.07	
AT/TT	581	460	0.98	(0.84, 1.13)			271	248	1.22	(0.99, 1.50)		
TERT-*CLPTM1L* (rs2853668)												
CC/CA	1810	1481	1		0.01		907	741	1		0.01	
AA	171	101	0.71	(0.55, 0.92)			90	46	0.62	(0.43, 0.90)		

[1]Odds ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, center, race, and sex.

Table 3

Interactions between *TERT* and BMI, NSAIDs, and risk of colon cancer

	BMI <25				BMI 25 to <30				BMI ≥30				
	Controls	Cases			Controls	Cases			Controls	Cases			
	N	N	OR	(95% CI)	N	N	OR	(95% CI)	N	N	OR	(95% CI)	Interaction *P*
TERT (rs10069690)													
CC	408	263	1.00		398	327	1.25	(1.01, 1.56)	222	198	1.37	(1.07, 1.75)	0.001
CT	308	193	0.97	(0.76, 1.23)	315	252	1.23	(0.98, 1.55)	136	187	2.08	(1.59, 2.74)	
TT	32	41	1.96	(1.20, 3.19)	69	44	0.96	(0.63, 1.45)	36	30	1.21	(0.73, 2.03)	
TERT (rs2242652)													
CC	491	317	1.00		493	405	1.25	(1.03, 1.52)	278	248	1.35	(1.08, 1.69)	0.012
CT/TT	258	181	1.09	(0.86, 1.38)	293	218	1.16	(0.92, 1.45)	117	164	2.17	(1.64, 2.86)	
TERT (rs2736118)													
AA	421	257	1.00		430	314	1.19	(0.96, 1.47)	186	213	1.85	(1.44, 2.39)	0.070
AG	287	200	1.14	(0.90, 1.45)	300	261	1.42	(1.13, 1.79)	181	158	1.41	(1.08, 1.84)	
GG	46	47	1.66	(1.07, 2.57)	66	55	1.33	(0.90, 1.98)	31	43	2.19	(1.34, 3.58)	
TERT (rs4246742)													
AA	527	367	1.00		576	423	1.05	(0.87, 1.27)	269	302	1.58	(1.28, 1.96)	0.018
AT/TT	230	137	0.85	(0.66, 1.09)	220	207	1.32	(1.04, 1.66)	130	114	1.23	(0.92, 1.64)	
	No Recent Aspirin/NSAID Use				Recent Aspirin NSAID Use								
TERT-CLPTM1L (rs2853668)													0.026
CC/CA	1064	998	1		731	467	0.68	(0.59, 0.79)					
AA	84	73	0.91	(0.65, 1.26)	86	27	0.33	(0.21, 0.52)					

[1] Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, center, race, and sex.