Variation in *TCF7L2* and Increased Risk of Colon Cancer

The Atherosclerosis Risk in Communities (ARIC) Study

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OBJECTIVE — The purpose of this study was to determine whether a variation in the transcription factor 7-like 2 (*TCF7L2*) gene, which influences diabetes risk, is associated with incidence of cancers.

RESEARCH DESIGN AND METHODS — We related diabetes and *TCF7L2* variation with occurrence of several common cancers in a prospective cohort study of 13,117 middle-aged adults initially free of cancer in 1987–1989. We assessed five single nucleotide polymorphisms (SNPs) in *TCF7L2* including the putative SNP (rs7903146) for diabetes. We identified incident cancers through 2000 via cancer registries, supplemented by hospital records.

RESULTS — Diabetes was associated marginally inversely with incidence of prostate cancer but not with incidence of colorectal, colon, lung, or breast cancer. The T allele of rs7903146 (frequency 30%) was associated with increased risk of colorectal cancer and, more specifically, colon cancer, with adjusted hazard ratios (95% CI) of 1.0 for CC, 1.25 (0.85–1.83) for CT, and 2.15 (1.27–3.64) for TT genotypes ($P_{trend} = 0.009$). *TCF7L2* variation also was associated with lung cancer incidence in whites but not blacks, but residual confounding by smoking may be present.

CONCLUSIONS — Subjects who were initially cancer-free and carrying certain genetic variants of *TCF7L2*, most notably the T allele of rs7903146, have an increased risk of colon cancer. This association appears to be an independent gene effect not explained by diabetes. Because the T allele of rs7903146 is common, if a causal link is established, this variant could account for a sizable proportion (~17% here) of cases of colon cancer in the general population.

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Whether type 2 diabetes is a cause of cancer is uncertain (1). Epidemiological studies have often implicated diabetes as a risk factor for several cancers, including endometrial cancer (1,2), pancreatic cancer (1,3), and colon cancer (1,4). However, often the classification of diabetes in prior cancer studies has been based on self-reported diabetes, not measured fasting glucose. Potential mechanisms connecting diabetes with increased cancer risk relate to obesity, physical inactivity, diet, and increased insulin and insulin-like growth factor-1. Diabetes, on the other hand, may be associated with decreased risk of prostate cancer (5,6), possibly because diabetic men tend to be hypoandrogenic (7,8). These epidemiological associations between diabetes and cancer, of course, might not be causal, but, rather, explained by shared underlying causes of diabetes and cancer.

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Abbreviations: *APC*, adenomatous polyposis coli; ARIC, Atherosclerosis Risk in Communities; SNP, single nucleotide polymorphism; *TCF7L2*, transcription factor 7-like 2.

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Recently a number of studies have shown that variations in the transcription factor 7-like 2 (*TCF7L2*) gene, previously called *TCF-4*, considerably affects risk of type 2 diabetes (9–12). Although the mechanisms linking *TCF7L2* variation with diabetes are still under investigation, one study reported that the *TCF7L2* risk variant, or its closest correlate, is the T allele of rs7903146 (13). A meta-analysis of >17,000 cases of diabetes reported that the T allele of rs7903146 was associated with a relative risk of 1.46 (95% CI 1.42–1.51) for diabetes. According to the concept of "Mendelian randomization " (14), if the T allele also were associated with increased cancer risk, it would support a causal link between diabetes and cancer. Alternatively, *TCF7L2* may affect cancer independently of diabetes, as the *TCF7L2* gene product is involved in the Wnt/β-catenin signaling pathway. Mutations involving the Wnt pathway and *TCF* target genes play a role in carcinogenesis, especially well documented for colon cancer (15,16). Besides being expressed in the colon and colon cancer, *TCF7L2* is expressed in normal mammary gland and prostate tissue and in cancers of these tissues (17–19) and non–small cell lung cancer (20).

We examined whether diabetes or variation in *TCF7L2* is associated with incidence of four common cancers (colorectal, prostate, female breast, and lung) in a large prospective cohort study, the Atherosclerosis Risk in Communities (ARIC) Study. Because diabetes has been associated epidemiologically more consistently with colorectal and prostate cancer than with lung and breast cancer, we hypothesized that *TCF7L2* variants increasing diabetes risk would be associated positively with colorectal cancer and negatively with prostate cancer incidence but would be unassociated with breast and lung cancer.

RESEARCH DESIGN AND METHODS

— The ARIC Study is a cohort study of cardiovascular disease in four U.S. communities. Between 1987 and 1989, 7,082 men and 8,710 women aged 45–64 years were recruited from

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Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); suburban Minneapolis, Minnesota; and Washington County, Maryland. The ARIC Study protocol was approved by the institutional review board of each participating university. After written informed consent was obtained, participants underwent a baseline clinical examination (visit 1). Follow-up examinations of the cohort occurred three times at intervals of roughly 3 years. The response rates for visits 2 (1990–1992), 3 (1993–1995), and 4 (1996–1998) were 93, 86, and 80%, respectively. The response to annual telephone interviews after visit 4 has been 94% of cohort survivors.

Risk factor measurements

Risk factors examined in these analyses were ascertained at visit 1, as described in detail in the ARIC Study manuals of operation (21). Participants were asked to fast before the clinical examination. Blood was drawn from an antecubital vein of seated participants into vacuum tubes containing EDTA (for measurement of lipids and DNA extraction) or a serum separator gel (glucose). Aliquots were stored at −70°C and were shipped to central laboratories for analyses. Serum glucose was assayed by a hexokinase/glucose-6-phosphate dehydrogenase method. Prevalent diabetes was defined as fasting glucose ≥126 mg/dl (22), a self-reported physician diagnosis of diabetes, or current treatment for diabetes.

BMI was assessed with the subject wearing a scrub suit and no shoes. Questionnaires assessed education, smoking status, number of cigarettes smoked per day and duration of smoking (pack-years computed), and usual alcohol consumption (grams per day). Level of sports physical activity was assessed by the Baecke Questionnaire (23).

In the ARIC Study five *TCF7L2* SNPs, initially reported to be associated with diabetes (rs7903146, rs12255372, rs7901695, rs11196205, and rs7895340) (9), were genotyped on stored DNA using the TaqMan system (Applied Biosystems, Foster City, CA). PCR primers and assay probes are available from the authors upon request.

Cancer ascertainment

During each clinical examination, participants were asked whether they had ever had a diagnosis of cancer. At each annual telephone interview, participants reported all hospitalizations. Among those not reporting cancer at the baseline visit, incident cancers were identified between 1 January 1987 and 31 December 2000 via linkage to state cancer registries and supplemented by the hospital records. This method and the high completeness of ARIC Study cancer ascertainment were described previously (6,24). For this analysis, we focused primarily on four site-specific common cancers (i.e., colorectal, lung, female breast, and prostate).

Data analysis and statistical methods

From the original ARIC cohort (n = 15,792), we excluded participants who did not want to participate in cancer research (n = 187), who denied permission for DNA testing (n = 79), who were in very small race/ethnic minority groups (n = 96), who did not provide sufficient data to determine baseline cancer status or who had a previous history of cancer (n = 877), who had missing DNA or *TCF7L2* genotypes (n = 927), or who had not fasted 8 h (n = 509). This left 13,117 in the cohort at risk.

Statistical analysis was performed by using SAS software (version 9.1; SAS Institute, Cary, NC). On the basis of previous reports on diabetes and cancer (1,4–6), we hypothesized that diabetes and *TCF7L2* variation would relate to colorectal and prostate cancer incidence but not to breast and lung cancer. Person-years at risk were calculated from the time of baseline clinical examination until the date of cancer diagnosis, death, loss to follow-up, or 31 December 2000, whichever occurred first. To explore possible confounding factors, means or prevalences of various risk factors were compared by *TCF7L2* genotype, using t tests or χ^2 tests. Crude cancer incidence rates (per 1,000 person-years) for *TCF7L2* genotypes were calculated. Adjusted hazard ratios (HRs) for the associations of the *TCF7L2* variants and diabetes with cancer incidence were calculated by using Cox proportional hazards regression. The test for trend in HRs modeled zero, one, or two risk alleles present. We tested for race by genotype interactions; with the exception of lung cancer, none was significant, so for other cancers we pooled blacks and whites. The proportional hazards assumption of the Cox model was found not to be violated by testing an interaction between *TCF7L2* variants and time. Our results focus primarily on SNP rs7903146, which is believed to be the functional SNP for diabetes or the closest correlate, but we comment in the text about associations in secondary analyses of the other four SNPs with cancer.

RESULTS — There were 433 incident cancers in 38,066 person-years of follow-up in blacks and 1,274 incident cancers in 109,701 person-years in whites, yielding crude incidence rates of cancer per 1,000 person-years of 11.4 in blacks and 11.6 in whites. As reported previously (6), in the ARIC Study, baseline diabetes was associated inversely with prostate cancer incidence (HR 0.71 [95% CI 0.49–1.03]), although at P = 0.08 for this somewhat smaller sample with genotype data (Table 1). Diabetes showed no significant association with colorectal, colon, breast, or lung cancer. Because diabetes developed in many participants during follow-up, we repeated the analysis for Table 1 but modeling diabetes as a time-dependent covariate. The results (not shown) were similar.

The race-specific frequencies of the five *TCF7L2* SNPs, which are available upon request, were in Hardy-Weinberg equilibrium. For rs7903146, the frequencies of CC, CT, and TT genotypes were 50, 42, and 8% in whites and 50, 41, and 9% in blacks. Linkage disequilibrium (r^2) between rs7903146 and the other four *TCF7L2* SNPs ranged from 0.44 to 0.97 in whites and 0.02 to 0.49 in blacks.

Associations of various risk factors with *TCF7L2* rs7903146 are shown in Table 2. As expected, diabetes prevalence showed a dose-response relation with the number of T alleles present. The number of T alleles was inversely related to BMI, as reported by others (13), and was positively related to smoking. No other risk factor was associated strongly with rs7903146 variation. The associations depicted in Table 2 were similar for whites and blacks.

As shown in Table 3, colorectal cancer was associated positively with the number of T alleles for rs7903146, with multivariable-adjusted HRs of 1.17 (95% CI 0.85–1.61) for CT and 1.56 (0.97–2.53) for TT, compared with CC. The number of rectal cancers was small, and the association for colon cancer alone was even stronger: HR 1.25 (95% CI 0.85–1.83) for CT and 2.15 (1.27–3.64) for TT compared with CC. These HRs were 1.19 and 2.01, respectively, in whites and 1.46 and 2.69 in blacks. The association with colon cancer largely persisted after adjustment for diabetes (not shown) or after exclusion of participants with baseline

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Table 1—*Crude incidence rate and adjusted HRs (95% CIs) of cancer by diabetes status at baseline, ARIC Study, 1987–2000*

	No. developing cancer	Person-years	Crude incidence rate	Age-, race-, and sex-adjusted HR (95% CI)	Fully adjusted HR (95% CI)*
Colorectal cancer					
No diabetes	157	137,764	1.14	1	1
Diabetes	23	15,023	1.53	1.18 (0.76–1.84)	1.13 (0.71–1.84)
Colon cancer					
No diabetes	110	137,967	0.80	1	
Diabetes	18	15,033	1.20	1.31 (0.79–2.16)	1.19 (0.70–2.03)
Lung cancer					
No diabetes	215	138,106	1.56	1	1
Diabetes	23	15,066	1.53	0.80 (0.52–1.24)	0.97 (0.62–1.51)
Breast cancer (women)					
No diabetes	305	75,124	4.06	1	1
Diabetes	36	8,023	4.49	1.07 (0.76–1.52)	1.08 (0.75–1.54)
Prostate cancer					
No diabetes	330	60,374	5.47	1	1
Diabetes	34	6,786	5.01	0.75 (0.53–1.07)	0.71 (0.49–1.03)

*Adjusted for baseline age (continuous), race (white or black), BMI (continuous), smoking status (current smoker or nonsmoker), pack-years (continuous), ethanol intake (continuous), sport index (continuous), education (< high school graduate or ≥ high school graduate), sex, and current hormone replacement therapy (male, female with no hormone replacement therapy, or female with hormone replacement therapy).

diabetes: respective HRs were 1.32 for CT and 1.75 for TT (P_{trend} = 0.05). When analyzed according to any regular use of aspirin during follow-up (assessed in 1994–1995 in 12,138 subjects), the multivariably adjusted HRs for colon cancer were similar among the 29% of subjects who had regularly used aspirin (1.23 for CT and 2.21 for TT) and among the nonusers (1.36 for CT and 2.21 for TT).

Lung cancer showed a significant positive association with the rs7903146 T allele in whites but not in blacks (Table 3). Breast and prostate cancers were not related to rs7903146T.

Associations between cancer and the other four *TCF7L2* SNPs are not presented but are available on request. Colon cancer incidence was associated positively, but more weakly (P_{trend} = 0.04–0.14), with the other four *TCF7L2* SNPs. Lung cancer in whites was associated (P_{trend} <0.05) with variants in three of the five SNPs. Breast and prostate cancers were not related to any *TCF7L2* SNPs.

CONCLUSIONS — Our main new finding was that variation in *TCF7L2* SNPs, particularly rs7903146, was moderately strongly associated with incidence of colon cancer in this cohort. The incidence rate of colon cancer was double in homozygotes for the T allele of rs7903146 compared with the CC homozygotes. There was a dose response of colon cancer incidence with the number of T alleles of rs7903146, and HRs were similar in blacks and whites. Some *TCF7L2* SNPs were also associated with lung cancer in whites but not in blacks. Although *TCF7L2* is a gene that affects risk of type 2 diabetes (9,13), diabetes was associated with no cancer examined, except inversely with prostate cancer, and the *TCF7L2* association with colon cancer was present when restricted to nondiabetic participants. Thus, the relation of *TCF7L2* variation with colon cancer appears to be an independent gene effect not explained by diabetes. Another study has reported that the T allele of rs7903146 is associated with increased colon cancer incidence but only among nonusers of aspirin (25). We did not observe such effect modification by aspirin.

The rs7903146 SNP resides within intron 3 in a 50,000-base pair region of the *TCF7L2* gene. Currently, the function of rs7903146 is unknown but is under investigation. Certainly, it may be another mutation in linkage disequilibrium with this SNP that affects gene function. In any case, a causal link between *TCF7L2* variation and colon cancer seems biologically plausible. This gene has a central role in the Wnt/β-catenin signaling pathway, which is strongly implicated in colon cancer etiology (15,16). Mutations in the adenomatous polyposis coli (*APC*) gene

Table 2—*Age-, race-, and sex-adjusted means and percentages of baseline risk factors by TCF7L2 genotype (rs7903146 SNP), ARIC Study, 1987–1989*

	TCF7L2 (rs7903146) SNP		
	CC	CT	TT
n	6,536	5,424	1,137
Prevalences			
Diabetes (%)	9.0	11.9*	13.7*
Current smoking (%)	24.6	26.0	27.9*
High school graduate (%)	77.7	75.2*	76.8
Current hormone replacement therapy use (women) (%)	23.3	22.0	20.9
Means			
BMI (kg/m^2)	27.8	27.6*	27.5*
Pack-years of smoking	309	317	336*
Ethanol intake (g/week)	42.1	42.3	42.9
Sport activity index (range 1–5)	2.44	2.44	2.42

*P < 0.05 compared with CC.

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Table 3—*Crude incidence rate and adjusted HRs (95% CI) of cancer by* TCF7L2 *genotype (rs7903146 SNP), ARIC Study, 1987–2000*

Cancer/genotype	No. developing cancer	Person-years	Crude incidence rate	Age-, race-, and sex-adjusted HR (95% CI)	Fully adjusted HR (95% CI)*
Colorectal cancer					
CC	80	76,707	1.04	1	1
CT	79	63,470	1.24	1.21 (0.89–1.65)	1.17 (0.85–1.61)
TT	21	13,314	1.58	1.50 (0.93–2.43)	1.56 (0.97–2.53)
P_{trend}					0.07
Colon cancer					
CC	54	76,841	0.70	1	1
CT	55	63,545	0.87	1.25 (0.86–1.82)	1.25 (0.85–1.83)
TT	19	13,320	1.43	2.02 (1.20–3.40)	2.15 (1.27–3.64)
P_{trend}					0.009
Lung cancer					
Whites					
CC	66	57,295	1.15	1	1
CT	90	47,139	1.91	1.69 (1.23–2.32)	1.63 (1.17–2.25)
TT	21	10,092	2.08	1.83 (1.12–2.99)	1.59 (0.96–2.63)
P_{trend}					0.008
Blacks					
CC	35	19,639	1.78	1	1
CT	22	16,459	1.34	0.75 (0.44–1.28)	0.75 (0.44–1.30)
TT	5	3,245	1.54	0.82 (0.32–2.10)	0.62 (0.22–1.76)
P_{trend}					0.22
Breast cancer (women)					
CC	177	42,318	4.18	1	1
CT	139	34,187	4.07	0.98 (0.78–1.22)	0.98 (0.78–1.23)
TT	26	7,140	3.64	0.87 (0.58–1.31)	0.87 (0.57–1.32)
P_{trend}					0.56
Prostate cancer					
CC	201	33,019	6.09	1	1
CT	131	28,401	4.61	0.78 (0.63–0.97)	0.80 (0.64–0.99)
TT	34	5,945	5.72	0.96 (0.67–1.38)	1.04 (0.72–1.50)
P_{trend}					0.33

*Adjusted for baseline age (continuous), race (white or black), BMI (continuous), smoking status (current smoker or nonsmoker), pack-years (continuous), ethanol intake (continuous), sport index (continuous), education (< high school graduate or ≥ high school graduate), sex, and current hormone replacement therapy (male, female with no hormone replacement therapy, or female with hormone replacement therapy).

cause colon cancer via this pathway. *APC* normally functions as a negative regulator of Wnt signaling by the destabilization of the β-catenin protein. Stabilized β-catenin interacts with *TCF7L2* and *LEF* to activate gene expression. Mutations in either *APC* or genes that modulate β-catenin can alter this regulatory relationship and lead to the activation or inhibition of genes that contribute to neoplasia (26). Although we had too few cases of rectal cancer to analyze separately, the association with *TCF7L2* rs7903146 seemed more specific for colon cancer alone than for grouped colorectal cancer. Further replication of our finding, including epidemiological studies of *TCF7L2* and colon adenomas, seems warranted. If the relation were causal, the estimated population risk of colon cancer attributable (27) to rs7903146 is 17%, given the genotype frequencies and hazard ratios observed here.

The association between *TCF7L2* variation and lung cancer in whites was unexpected, because smoking is clearly the overwhelming cause of lung cancer. Although the Wnt/β-catenin pathway may be involved in lung cancer, this involvement has only limited documentation (20). Also unexpected was the association in the ARIC Study between *TCF7L2* rs7903146 and smoking status and pack-years. To our knowledge, no previous study has reported this association, so it may be a chance or spurious finding. We adjusted the association between *TCF7L2* and lung cancer for smoking variables, but it is possible that there is residual confounding by smoking. Given that an association of *TCF7L2* with lung cancer was not hypothesized and found only in whites, this finding should be viewed cautiously.

Strengths of this study were the prospective design and highly complete ascertainment of cancer. The main limitations were the moderate number of cancer events and absence of detail (e.g., histologic review, stage, and biomarkers such as prostate-specific antigen) on them. Further, candidate gene studies often yield false-positive results. Thus, even though the associations we identified seem biologically plausible, they need replication.

In summary, subjects who were initially cancer-free and carried certain common genetic variants of *TCF7L2*, most notably the T allele of rs7903146, have an increased risk of colon cancer. This association appears to be an independent gene effect, not explained by diabetes. Because

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the T allele of rs7903146 is common, if a causal link is established, this variant could account for a significant proportion of cases of colon cancer in the general population.

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