Polymorphisms of the Dopamine Receptor Gene

**DRD2** and Colorectal Cancer Risk

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**Abstract**

Sporadic colorectal cancer is considered a multifactorial disease in which multiple exposures interact with the individual genetic background resulting in risk modulation. Recent experimental data suggest a role of dopamine and dopamine receptors in the control of proliferation of the cells of colon and gastrointestinal tract. To investigate whether polymorphisms within dopamine receptors genes could have a role in modulating the risk of sporadic colorectal cancer, we did a case-control association study and genotyped 370 cases and 327 controls for seven single-nucleotide polymorphisms (SNP) of *DRD2* (−141Cdel, 957T>C, TaqIB, TaqIA, 1412A>G, S311C, and 3208G>T) by a microarray-based technique. Three SNPs within *DRD2* were associated with colorectal cancer, with a maximum odds ratio of 2.28 (95% confidence interval, 1.38-3.76) for carriers of the functional SNP −141Cdel. The haplotype which includes −141Cdel, together with the variants 957C and 1412G, shows an odds ratio of 2.86 (95% confidence interval, 1.58-5.18), as compared with the most frequent haplotype. The SNPs within *DRD2* associated with colorectal cancer are known to be related to reduced levels of D2 dopamine receptor. Thus, our data point to a possible role of dopamine receptor *DRD2* in modulating the risk of colorectal cancer. Future studies on dopamine receptor-mediated signal transduction may provide new insight into the mechanisms of colorectal cancer and suggest new therapeutic strategies. (*Cancer Epidemiol Biomarkers Prev* 2005;14(7):1633–8)

**Introduction**

Sporadic colorectal cancer is considered to be a multifactorial disease, in which multiple exposures to endogenous factors and dietary carcinogens interact with individual genetic background in a complex manner resulting in modulation of the risk. Thus, many case-control association studies have been done, focusing on genes affecting the metabolism of dietary carcinogens. The polymorphic enzymes involved in phase I (e.g., CYP1A1) and phase II (e.g., NAT2) metabolism of xenobiotics (extensively reviewed in refs. 1, 2) were among the first candidates to be studied. However, little is known about endogenous factors that could alter the physiology of the colon, leading to an increased risk of cancers. Beyond xenobiotic metabolism genes, some studies have focused on genes regulating cellular growth (1) because slightly enhanced proliferation might lead to an increased rate of fixation of mutations, genes of the DNA repair system (3) because a slightly impaired capacity of processing DNA lesions may lead to increased accumulation of mutations, and genes affecting the local microenvironment (2, 4, 5) as they might favor proliferation or oxidative stress in the tissue.

Little attention has been paid to dopamine and dopamine receptors, although dopamine has been shown to regulate the growth of cells of the gastrointestinal tract (6) and to exert a protective effect for stomach and intestine against experimental carcinogenesis in animal models (7). It has also been shown that the malignant human colon tissue has a decreased dopamine content as compared with the normal tissue, and this reduction has been suggested to be linked to a decreased expression of dopamine receptors, such as those of D2 type (8). Thus, to seek novel mechanisms in the etiology of human colorectal cancers, we investigated whether the risk of colorectal cancer is modulated by genetic variations within the dopamine receptor gene *DRD2*. Notably, there are several studies indicating that the D2 dopamine receptor gene bears polymorphisms that affect the function of the protein or its expression (9-11), and these are associated with a wide range of neurologic, psychiatric, or behavioral conditions (including Parkinson’s disease, schizophrenia, schizoid behavior, and addiction to smoking and alcohol; ref. 12). These variants are also associated with an altered response to bromoperidol, an antagonist for D2-like dopamine receptors (13), and bupropion, a dopamine reuptake inhibitor (14). Furthermore, they were associated also with an altered binding of dopamine in caudate, putamen, and accumbens nuclei (15).

To investigate whether functional polymorphisms within *DRD2* could have a role in modulating the risk of sporadic colorectal cancer, we analyzed the genotypes obtained in 370 cases and 327 controls for seven single nucleotide polymorphisms (SNP) of *DRD2* (−141Cdel, 957T>C, TaqIB, TaqIA, 1412A>G, S311C, and 3208G>T).
Materials and Methods

Study Population. A case-control study was conducted to assess gene-environment interactions in relation to colorectal cancer risk. Cases were patients with a new diagnosis of colorectal adenocarcinoma attending a University Hospital in Barcelona, Spain, between January 1996 and December 1998. This study includes those 357 (72% of eligible) who could be interviewed and who provided biological samples of sufficient quality for genetic analysis. Refusals were 2% of eligible, whereas 14% could not be interviewed because they either had died, had mental or some other impairment, or were released without being approached and could not be traced. Finally, 12% were interviewed but did not provide biological samples. These lost cases were similar to those included with respect to age, sex, tumor location, and extent. To avoid selection bias, the criterion for inclusion of cases was that the reason for the current admittance to the hospital should be a new disease (not previously diagnosed) for that patient. This criterion was used to avoid inclusion of patients with chronic diseases, who might be repeatedly admitted to hospital and modify their habits because of their disease. The controls (n = 327, 69.4% of eligible) were people living in the same area and representative of the general population, randomly enrolled among patients admitted to the same hospital during the same period of time. Refusals were 7% of eligible, whereas 5% could not be interviewed because of mental or other impairment. Finally, 87 (18.6%) were interviewed but did not provide a blood sample. For some polymorphisms, numbers do not sum up to the totals of controls or cases due to genotyping failure. All samples that did not give a reliable result in the first round of genotyping were resubmitted to additional genotyping. Data points that were still not filled after this procedure were left blank. The Ethics Committee of the hospital cleared the study protocol and all individuals gave written informed consent to participate and for genetic analysis to be done on their samples. More details on the study population, composition, and interviews were given elsewhere (4).

Genotyping. Genomic DNAs were amplified to enrich the fragments carrying the seven SNPs by using specific primer pairs, as described elsewhere (16-19). Genotyping was done with a microarray setup with the Arrayed Primer EXTension (APEX) approach. Arrayed Primer EXTension consists of a sequencing reaction primed by an oligonucleotide anchored with its 5' end to a glass slide and terminating just one nucleotide before the polymorphic site. A DNA polymerase extends the oligonucleotide by adding one fluorescently labeled deoxynucleotide triphosphate complementary to the variant base. Reading the incorporated fluorescence identifies the base in the target sequence. This method is suitable not only for SNPs but also for small insertion/deletion polymorphisms (20). Because both sense and antisense strands are sequenced, two oligonucleotides were designed for each polymorphism. In general, two 30-mers, one for each strand, complementary to each side of the polymorphism were designed with their 3' end pointing towards the polymorphism. The flanking sequences and their related APEX oligonucleotides are available on the web (http://www-gan.iarc.fr/MetaboChip.html). Five-prime (C-12) aminolinker oligonucleotides were synthesized by Sigma Genosys (Sigma-Genosys Ltd, Cambridge, United Kingdom) and spotted onto silanized slides as reported elsewhere (20, 21). PCR products were pooled, purified, concentrated using Millipore Microcon MY30 columns, and fragmented as reported in detail elsewhere (18). For single-base extension reaction, fragmented PCR products were incubated onto the slides together with the fluorescently labeled deoxynucleotide triphosphates (4 x 50 pmol), 10× buffer, and 4 units of Thermo Sequenase (Amersham Bio-

sciences, Uppsala, Sweden) as previously reported (18). Slides were imaged by a Genorama-003 four-color detector equipped with Genorama image analysis software (Asper Biotech, Tartu, Estonia). Fluorescence intensities at each position were converted automatically into base calls by the software under the supervision of an operator. In case of more than one signal present on a given position, only the main signal was considered, when the intensity of the weaker signal was lower than 10% of the main signal.

Genotyping for the -141Cdel SNP was also repeated with the 5' nuclease (a.k.a. TaqMan) assay. PCR primers sequences were as follows: DRD2.-141Cdel.F, AAACAGGGATGCCG-GAATC; DRD2.-141Cdel.R, CAACAAAGGAAGCTGAACTC. The following TaqMan probes were used: DRD2.-141C, FAM-TAMRA-CCCCCTCTACCCGTCAGGC; DRD2.-141del, HEX-TAMRA-CAACCCCTCTACCGGTACAGC.

TaqMan genotyping was done using the standard protocol, as recommended by Applied Biosystems, and results were read on an ABI 7900HT instrument (Applied Biosystems, Foster City, CA).

Interviews. Cases and controls were interviewed by trained personnel using a structured questionnaire. A dietary history questionnaire, previously developed and validated in the framework of the European Prospective Investigation into Cancer and Nutrition study (22), focused on average food consumption 1 year before diagnosis. Food groups based on bromatological properties were calculated from reports of items consumed. Other risk factors measured were body mass index at diagnosis and 10 years before, life-long history of drug use, with special emphasis on nonsteroidal anti-inflammatory drug, tobacco, and alcohol use. Family history of neoplasms were collected for first- and second-degree relatives. Cases belonging to familial adenomatous polyposis were excluded but three cases that fulfilled the criteria of Amsterdam for hereditary nonpolyposis colorectal cancer were not excluded.

Statistical Analysis and Haplotype Reconstruction. Each polymorphism was tested in controls to ensure the fitting with Hardy-Weinberg equilibrium. To test the hypothesis of association between genetic polymorphisms and colorectal cancer, multivariate methods based on logistic regression analyses were used. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each group compared with the class with the lowest level of exposure (set as having risk = 1). For polymorphisms, homozygosity for the more frequent allele among controls was set as the reference class. Tests for linear trend of ORs were calculated using the categorized variable as quantitative after assigning a linear score to each ordered category. For polymorphisms, the homozygote for the more frequent allele (reference) was given a score of 1, the heterozygote score 2, and the homozygote for the rarer allele score 3. P values were derived from likelihood ratio tests.

Analyses were done under a codominant model (three genotypes separated). Also a dominant model (heterozygotes grouped with the homozygotes for the rarer allele) or a recessive model (heterozygotes grouped with the homozygotes for the common allele) was fitted when the similarity of the ORs suggested they might fit better than the codominant model. All analyses were adjusted for age and sex. A significance level of 5% (two sided) was used for the analyses. Haplotypes were reconstructed using the software PHASE version 2 (23), and a global test of hypothesis for the gene was carried out, followed by contrasts for specific haplotypes.

Results.

The main characteristics of the population under study are summarized separately by cases and controls in Table 1.
Positive familial history of colon cancer, high energy intake, and alcohol consumption were increased with increased risk of colorectal cancer in this population, whereas use of nonsteroidal anti-inflammatory drugs was associated with a reduced risk of colorectal cancer.

The results of the SNP analyses are presented in Table 2. We observed an association between −141Cdel, TaqIB, and 957C of DRD2 and colorectal cancer. Polymorphism −141Cdel was the one with the lowest P value (P < 0.001). This variant is rare, and only four homozygotes (two cases and two controls) were detected in the sample. The dominant model confirmed the association (OR, 2.8; 95% CI, 1.38-5.76). To confirm the results for −141Cdel, we regenotyped blindly all cases and controls with the 5′ nuclease assay (TaqMan), and we obtained the same results. Increased risks of cancer were observed in −141Cdel carriers also when the samples were stratified for colon and rectum (OR, 3.35; 95% CI, 1.67-6.7 and OR, 2.22; 95% CI, 0.97-5.09, respectively).

In our sample set, the TaqIB polymorphism was also associated with an increased risk of colorectal cancer and showed the highest OR for the variant homozygotes. This suggested a recessive model for this SNP (OR, 4.7; 95% CI, 1.1-21.8). However, the 957C allele, which was also associated with an increased risk of colorectal cancer, was better explained by a dominant model (OR, 1.41; 95% CI, 1.01-1.96).

To investigate further these associations, we analyzed the haplotypes of DRD2, composed by the seven DRD2 SNPs, taken in their physical order (Table 3). Haplotype frequencies found in our control population agree closely with those previously reported (24, 25). Haplotype 5 was the only one significantly associated with colorectal cancer, conferring a risk of 2.86 (95% CI, 1.58-5.18) compared with the most common haplotype. Haplotype 5 includes alleles −141Cdel, 957C, and 1412G. Because haplotype 2 also carried the variants 957C and 1412G, but not −141Cdel, and haplotype 2 was unrelated to colorectal cancer, it seemed that the risk could be related to −141Cdel or a cooperative effect of these variants. The association between 957C and colorectal cancer observed for the dominant models could be due to a linkage disequilibrium with the −141Cdel polymorphisms. TaqIB polymorphism was also found in only one haplotype (number 3), weakly associated with colorectal cancer (OR, 1.33; 95% CI, 0.93-1.91). Overall, the haplotype reconstruction suggests that analysis of the most studied polymorphisms TaqIA and S311C may not be sufficient for revealing associations with complex diseases, and indicates an effect of −141Cdel polymorphism, and also a weak but appreciable effect of TaqIB, in affecting the risk for colorectal cancer.

The association between polymorphism −141Cdel and colorectal cancer was explored in relation to other relevant variables for colorectal cancer to exclude confounding and detect interactions. Polymorphism −141Cdel was unrelated to body mass index, alcohol and smoking habits, dietary food groups, positive family history of colorectal cancer, and long-term intake of drugs, including nonsteroidal anti-inflammatory drugs and drugs used for psychiatric indications (neuroleptics and antidepressants). In Table 4 we report the distribution of the main demographic variables across the −141Cdel genotypes showing the lack of
In this study we have found that polymorphisms in DRD2 are associated with an increased risk of colorectal cancer. Previous studies have shown that these polymorphisms may have an effect on the function of the DRD2 receptor. The deletion −141Cdel in the 5′ untranslated region of DRD2 was reported to be associated with a reduction of roughly 20% to 40% in basal levels of receptor expression as compared with the “wild-type,” and it is considered a functional polymorphism (26), although not all the experimental evidences were able to confirm such a finding (11). The 957T>C polymorphism codes for the silent change proline to proline at codon 319. It has been suggested that this polymorphism is associated with alterations of mRNA folding, mRNA stability, and translation of the protein (9). Finally, TaqIB (A>G in intron 1) has been associated with a reduction of receptor density in vitro (27). TaqIB, TaqIA, and −141Cdel polymorphisms have been associated with several neurologic disorders and addictive behaviors (12, 28, 29).

### Table 3. Haplotype structure and statistical analyses for SNPs within DRD2

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Controls Only</th>
<th>Cases Only</th>
<th>OR* (95% CI)</th>
<th>Promoter</th>
<th>Intron 1</th>
<th>Intron 5</th>
<th>Exon 7</th>
<th>Exon 7</th>
<th>Exon 8</th>
<th>3′ Untranslated region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td>TaqIB</td>
<td>S311C</td>
<td>957T&gt;C</td>
<td>1412A&gt;G</td>
</tr>
<tr>
<td>1</td>
<td>347 (58.2)</td>
<td>376 (54.7)</td>
<td>1.00 NA NA</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>116 (19.5)</td>
<td>130 (18.9)</td>
<td>1.04 1.04</td>
<td>1.40</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>G</td>
</tr>
<tr>
<td>3</td>
<td>62 (10.4)</td>
<td>89 (12.9)</td>
<td>1.33 0.84</td>
<td>1.46</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>29 (4.9)</td>
<td>27 (3.9)</td>
<td>0.84 0.7</td>
<td>1.16</td>
<td>C</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>15 (2.5)</td>
<td>44 (6.4)</td>
<td>2.86 2.86</td>
<td>5.18</td>
<td>del(C)</td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>G</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>11 (1.8)</td>
<td>8 (1.2)</td>
<td>0.69 0.69</td>
<td>1.73</td>
<td>C</td>
<td>G</td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>All others</td>
<td>16 (2.7)</td>
<td>14 (2.0)</td>
<td>0.81 0.81</td>
<td>1.69</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE: SNPs are aligned from the 5′ to the 3′ of the gene. The haplotypes with increased risk as compared with the most common haplotype are in bold.

### Table 4. Main demographic and characteristic variables of the analyzed population distributed across −141Cdel genotypes

<table>
<thead>
<tr>
<th></th>
<th>Controls only</th>
<th>Cases + controls</th>
<th>OR* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>141 (53)</td>
<td>10 (40)</td>
<td>1</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>123 (47)</td>
<td>15 (60)</td>
<td>1.75 (0.76-4.02)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (25)</td>
<td>5 (20)</td>
<td>1</td>
<td>0.46</td>
</tr>
<tr>
<td>25-34</td>
<td>75 (28)</td>
<td>11 (44)</td>
<td>1.98 (0.66-5.96)</td>
<td>0.46</td>
</tr>
<tr>
<td>35-44</td>
<td>52 (22)</td>
<td>4 (16)</td>
<td>0.95 (0.25-3.65)</td>
<td>0.46</td>
</tr>
<tr>
<td>50-69</td>
<td>65 (25)</td>
<td>5 (20)</td>
<td>1.01 (0.28-3.61)</td>
<td>0.46</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>151 (57)</td>
<td>15 (60)</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>72 (27)</td>
<td>5 (20)</td>
<td>1.60 (0.33-7.77)</td>
<td>0.48</td>
</tr>
<tr>
<td>Smoker</td>
<td>41 (16)</td>
<td>5 (20)</td>
<td>2.51 (0.57-11)</td>
<td>0.48</td>
</tr>
<tr>
<td>Alcohol (duration, y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>119 (45)</td>
<td>15 (60)</td>
<td>1</td>
<td>0.14</td>
</tr>
<tr>
<td>0, 39</td>
<td>62 (23)</td>
<td>7 (29)</td>
<td>1.11 (0.38-3.24)</td>
<td>0.14</td>
</tr>
<tr>
<td>40, 80</td>
<td>83 (31)</td>
<td>3 (12)</td>
<td>0.31 (0.07-1.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>189 (72)</td>
<td>16 (64)</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>Ever</td>
<td>75 (28)</td>
<td>9 (36)</td>
<td>1.48 (0.62-3.55)</td>
<td>0.48</td>
</tr>
<tr>
<td>Familial history of cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>149 (56)</td>
<td>10 (40)</td>
<td>1</td>
<td>0.46</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>13 (5)</td>
<td>2 (8)</td>
<td>1.87 (0.36-9.79)</td>
<td>0.46</td>
</tr>
<tr>
<td>Other cancers</td>
<td>102 (39)</td>
<td>13 (52)</td>
<td>1.71 (0.7-4.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Energy intake (cal/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>103 (40)</td>
<td>13 (52)</td>
<td>1</td>
<td>0.41</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>81 (31)</td>
<td>7 (28)</td>
<td>0.75 (0.27-2.04)</td>
<td>0.41</td>
</tr>
<tr>
<td>Other cancers</td>
<td>75 (29)</td>
<td>5 (20)</td>
<td>0.62 (0.19-2.04)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

NOTE: Distributions are calculated both in controls and in the whole sample set.

*OR adjusted for sex + age.

†OR adjusted for sex + age + case/control status.
analysis of haplotypes suggests that –141Cdel is responsible for most of the associations found here, a cooperative effect of the other SNPs cannot be ruled out.

In our study, no associations were found between DRD2 polymorphisms and total daily caloric intake, body mass index, constipation, and use of laxatives (data not shown). These facts suggest that the association between DRD2 polymorphisms and colorectal cancer is not related to obesity or reduced intestinal motility. In addition, there are no significant associations between alcohol or smoking habits or specific foods consumed by the investigated subjects and these polymorphisms (data not shown). So, why would polymorphisms within the D2 type receptor be associated with colorectal cancer?

Dopamine is an important neurotransmitter for the epithelium of the gastrointestinal tract, and significant amounts of dopamine are produced within it (30). Dopamine receptors are present throughout the digestive tract (8). Dopamine protects the stomach against ulceration and the entire gastrointestinal tract from other types of mucosal stress, including that caused by carcinogens (6, 7, 31). In an animal model, it has been shown that the dopamine antagonist haloperidol increases the mitotic activity of gastrointestinal epithelium (32), suggesting that dopamine plays a modulatory role in the regulation of mitotic activity. Dopamine acts through G-protein–coupled D2 receptors to affect the amount of intracellular cyclic AMP (33), which in turn is an inhibitor of the mitotic activity of colorectal cancer cells (34). Interestingly, the content of dopamine within malignant human colon tissue is reduced 3- to 10-fold compared with normal tissue and it parallels the stages of the tumor (8). Similar reductions are also observed for the dopamine binding sites and the intracellular pool of cyclic AMP, suggesting that reduced inhibition of cellular growth could occur through a progressive loss of dopamine receptors (8). This fact is also corroborated by the observation that GH3 cells lacking endogenous DRD2 and resistant to dopamine-induced apoptosis, when stably transfected with either the long or short cDNA isoforms of DRD2, show a dopamine-dependent apoptosis via the p38 mitogen-activated protein kinase and extracellular signal-regulated kinase pathway (35). Thus, it is conceivable that genetic polymorphisms causing a reduced density of dopamine receptors D2 lead to reduced levels of cyclic AMP within the colonic mucosa cells, reducing the inhibition of the cellular growth or altering the intracellular apoptotic signaling, and thus making the cells more prone to progress through the cell cycle (i.e., increasing the risk of cancer).

An estimate of the probability of false discoveries can be calculated for significant results (36). This method is based on a Bayesian framework and requires providing a subjective estimate of the prior probability that a result is really positive. This prior probability, combined with the P value observed in the study, determines the posterior probability that is called the false-positive result probability. The association between DRD2 polymorphisms and colorectal cancer has never been reported, but many studies have shown the functional effects of DRD2 polymorphisms and the association of these polymorphisms with other disease states. We could assume that the prior probability that DRD2 polymorphisms are also associated with colorectal cancer could be low, in the range of 0.1% to 1%. This results in a false-positive result probability below 50% for the 0.1% prior probability, which could be considered the threshold of noteworthiness, and a false-positive result probability below 10% for the 1% prior probability. Thus, it is likely that our findings did not occur by chance. Rather, they reinforce the idea that dopamine receptors are important in the etiology of colorectal cancer. Future studies on dopamine receptor–mediated signal transduction in colon cancer cells and its influence on growth factors and oncogenes may provide new insight into the molecular mechanisms of the disease as well as suggest new therapeutic approaches and strategies for chemoprevention.

Acknowledgments
We thank Dr. John Cheney (IARC) for English revision.

References
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