Genetic Variation in 3-Hydroxy-3-Methylglutaryl CoA Reductase Modifies the Chemopreventive Activity of Statins for Colorectal Cancer

Steven M. Lipkin1, Elizabeth C. Chao2, Victor Moreno3,4,7, Laura S. Rozek3,5, Hedy Rennert8, Mila Pinchev8, Diana Dizon2, Gad Rennert8, Levy Kopelovich9, and Stephen B. Gruber3,4,6

Abstract
Genetic variation in 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis, modifies the effect of statins on serum cholesterol levels. Long-term use of statins is associated with a reduced risk of colorectal cancer (CRC) in some, but not all, studies. We genotyped variants in 40 candidate genes important for cholesterol synthesis and metabolism in a population-based case-control study of CRC involving 2,138 incident cases and 2,049 population-based controls. We identified a single-nucleotide polymorphism in the HMGCR gene that significantly modified the protective association between statins and CRC risk. Compared with nonusers, the unadjusted odds ratio of CRC among statin users with the A/A genotype of rs12654264 in HMGCR was 0.3 (95% confidence interval, 0.18-0.51) and among statin users with the T/T genotype was 0.66 (95% confidence interval, 0.41-1.06; P-interaction = 0.0012). This genetic variant (A/A genotype of rs12654264) also was associated with lower serum levels of low-density lipoprotein among all cases and controls. In colon cancer cell lines, the reduction in cholesterol levels after statin treatment was substantially stronger in cells carrying the A/A genotype, and this difference was related to alternative splicing involving the HMGCR statin-binding domain. We anticipate that these data may advance the development of personalized statin use for reducing the risk of cancer as well as cardiovascular disease among the approximately 25 million people currently using statins worldwide. Cancer Prev Res; 3(5): 597–603. ©2010 AACR.

Introduction
Statins are used by more than 25 million individuals worldwide for reducing the risk of cardiovascular disease (1). Statins are effective lipid-lowering agents that inhibit 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR) by binding directly to it and thereby reduce endogenous cholesterol synthesis. There is substantial variability in interindividual response to statin therapy for cardiovascular disease (2–4), and pharmacogenetic differences are thought to contribute significantly to this variability (5–10). Genetic analyses of subjects from the Pravastatin Inflammation CRP Evaluation (PRINCE), Cholesterol and Pharmacogenetics (CAP), Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22), and other cardiovascular risk-reduction clinical trials showed that pharmacogenetic variants in HMGCR and KIF6 influence the degree of lipid reduction during statin therapy (5, 11, 12). Similar analyses of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) showed that a common variant in SLCO1B1 is significantly associated with an increased risk of statin-induced myopathy (13).

Cancer chemoprevention is increasingly moving from the realm of clinical trials to clinical practice. The U.S. Food and Drug Administration has approved human papillomavirus vaccination for girls and young women to reduce their risk of cervical intraepithelial neoplasia and cancer, tamoxifen and raloxifene for reducing the risk of breast cancer among women at an increased risk, and celecoxib in the setting of colorectal adenomas in familial
adenomatous polyposis patients, who are at a very high risk (14). The latter three agents have adverse effects, however, limiting their public acceptance, and so the broad application of chemoprevention requires carefully optimizing risk reduction while minimizing toxicity.

Individual and combined statins have cancer chemopreventive activity in multiple preclinical models of colorectal cancer (CRC; refs. 15–20). A population-based case-control study that found a reduced risk of CRC among statin users (21) led to several studies that tested the hypothesis that statins are associated with a reduced risk of CRC in humans. In addition to a recent case-control study showing an inverse association between filled statin prescriptions and colon cancer [odds ratio (OR), 0.88; 95% confidence interval (95% CI), 0.83–0.93; ref. 22], nine case-control studies in a recent meta-analysis showed statins to be associated with a significant, but modest, reduction in the risk of CRC (relative risk, 0.91; 95% CI, 0.87–0.96; ref. 23). Although similar in magnitude, the reduced risk in six randomized clinical trials (relative risk, 0.95; 95% CI, 0.80–1.13) and three cohort studies (relative risk, 0.96; 95% CI, 0.84–1.11) was not statistically significant (23). A more recent cohort study found no evidence of a reduced CRC risk among regular statin users, but it could not exclude a reduced risk among long-term users (incident rate ratio, 0.89; 95% CI, 0.70–1.13) or among long-term high-dose statin users (incident rate ratio, 0.69; 95% CI, 0.37–1.28; ref. 24).

To test the hypothesis that the same type of pharmacogenetic variation that influences response to statin therapy in the setting of cardiovascular disease might also modify the statin-CRC risk association, we measured single-nucleotide polymorphisms (SNP) in 40 genes, including HMGCR. We tested this hypothesis in biospecimens and the epidemiologic/clinical data set of a population-based case-control study of CRC that previously had shown an association between long-term use of statins and reduced CRC risk (21).

Materials and Methods

Case-control study

The Molecular Epidemiology of Colorectal Cancer (MECC) study is a population-based case-control study of incident CRC in northern Israel. In brief, cases were eligible if they were diagnosed with pathologically confirmed, invasive CRC between March 31, 1998 and March 31, 2004 and who lived in a geographically defined area of Northern Israel. Controls were identified from the same source population using the Clalit Health Services database, covering ~70% of the older population. Controls were individually matched to cases by year of birth, gender, primary clinic location, and Jewish and Arab ethnicity. Potential controls were excluded if they had a prior history of CRC. Participants provided written informed consent at the time of enrollment. Interviews assessed demographic information, personal and family history of cancer, reproductive history and medical history, medication use, health habits, and a food-frequency questionnaire. Diagnoses of CRC were confirmed by standardized pathology review by one pathologist. Blood samples were drawn from participants at the time of diagnosis (cases) or time of interview (controls). Genomic DNA was extracted from theuffy coat, and lymphocytes were isolated on a Ficoll gradient; the DNA was quantified and stored at –20°C. The Institutional Review Boards at the Carmel Medical Center and the University of Michigan approved all procedures. Methodologic details have been previously described in detail (21).

Exposure data

Within the context of a comprehensive epidemiologic questionnaire administered in person by trained interviewers, participants named each medication they had used for more than 5 years by recall, and statins were abstracted from this list. Duration of statin use was not available; a validation study, however, showed excellent correspondence between self-reported use and prescription records. Prescription records for statins were evaluated in all individuals who were invited to participate in the study in the year before diagnosis for cases and the year before being approached for the study for controls to evaluate potential differences between participating and non-participating cases and controls, as previously described (21). History of medical conditions was measured by asking if participants had ever been diagnosed with any of 15 medical conditions including hypercholesterolemia and ischemic heart disease.

Statistical methods

Logistic regression was used to assess the association between genotypes, statins, and CRC to adjust for confounding and to evaluate potential effect modification. Unconditional models were used to avoid discarding matched pairs lost due to missing values. Sensitivity analyses were done to explore potential differences when using a conditional model and adjustment for potential confounders. No bias was observed, but there was lower precision in the estimates. Thus, unadjusted ORs derived from unconditional logistic regression are reported. We adjusted for multiple comparisons in the discovery phase of the study by Bonferroni correction of the P values using the number of genes as independent hypotheses (P < 0.0013 was considered to be statistically significant). The minor allele was always designated as the risk allele by convention. Genotypes and haplotypes were assessed specifying a log-additive model, which describes the relative risk for each additional copy of the minor allele. Statistical analyses took advantage of the gains in efficiency that can be achieved by “case-only” analysis to identify evidence of effect modification (25). Given that the genotypes are independent of the exposure use among controls, the test for association between the genotype and the exposure among cases is a test for interaction that is more powerful than the test that uses both cases and controls.
The exposure of interest for case-only analyses was long-term statin use and the risk modification by HMGCR genotypes and haplotypes specifying a log-additive model. The analysis of lipid levels was done using linear regression models.

A panel of 300 anonymous SNPs useful for population stratification analysis was analyzed in these subjects in relation to other larger genotyping project. No relevant population structure was identified that could not be explained by reported ethnicity. The potential confounding of this variable was rejected after a sensitivity analysis and was not used in the models to maximize efficiency. Statistical analyses were done using SAS v. 9.1 (SAS Institute) and R v. 2.6.0 (R Foundation for Statistical Computing). All reported P values are two-tailed. Haplotype analyses were accomplished using the haplo.stats package in R and the SNPstats web tool (26).

**SNP selection and genotyping**

Sixty-one candidate genes related to cholesterol biosynthesis and metabolism were initially selected for evaluation. These were prioritized to select 40 genes for genotyping. Maximally informative hSNPs were chosen for each gene using HaplOTagger. SNPs were genotyped using Illumina Beadstation and BeadExpress platforms. Data were analyzed using unsupervised Illumina BeadStation SNP calling automated routines, and the distribution of genotypes was compared with that expected from Hardy-Weinberg equilibrium. Genotypes in HMGCR were further confirmed with a second platform in at least 1% of samples.

**Cell culture studies and HMGCR mRNA isoform quantification**

To understand the potential mechanisms that could explain our finding that genetic variation in HMGCR modifies the chemopreventive potential of statins, we cultured CRC cells with atorvastatin using previously described methods (27). We then tested the hypothesis that this phenomenon might be explained by alternative splicing. In this experiment, we measured the levels of both full-length HMGCR and HMGCR v1 transcripts (28). Total RNA was isolated from cultured cells (Trizol, Invitrogen). mRNA levels of the full HMGCR length gene were measured with three TaqMan assays spanning three regions of the gene: exons 6 to 7, exons 12 to 13, and exons 12 to 14. This allowed us to quantify the total, full-length, and HMGCR v1 transcripts and serially diluted standards of each. Probes were purchased from Applied Biosystems. Each TaqMan reaction was done in triplicate or quadruplicate on the ABI Prism 7900HT SDS and 125 ng cDNA as previously done (28).

**Results**

Cases and controls had similar baseline characteristics (Table 1). Weight was recorded by self-report, as estimated 1 year before diagnosis for cases and at the time of inter-

<table>
<thead>
<tr>
<th>Cases Controls</th>
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<tbody>
<tr>
<td>Age (y), mean (SD) 70.1 (11.8) 70.9 (11.7)</td>
</tr>
<tr>
<td>Weight (year before dx), mean (SD) 75.0 (14.8) 73.7 (13.9)</td>
</tr>
<tr>
<td>Body mass index, mean (SD) 27.4 (6.1) 27.0 (5.9)</td>
</tr>
<tr>
<td>HDL, mean (SD) 50.7 (12.7) 50.7 (12.3)</td>
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</table>
| Total cholesterol, mean (SD) 204.1 (38.7) 203.7 (36.4) | *Cases and controls were matched for gender and age (within 1 year).*

View for controls. Serum lipids measured before diagnosis were available from electronic medical records for 408 of 2,138 cases (19.1%) and 729 of 2,049 controls (35.5%), and high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol were similar in cases and controls.

SNPs in 40 genes, including 6 SNPs within HMGCR, were genotyped in CRC cases and controls. We first considered whether genetic variation in any cholesterol synthesis or metabolism genes was associated with risk of CRC. However, we did not find any significant relationships between individual SNPs and CRC risk after adjustment for multiple comparisons.

We then tested whether genetic variation in HMGCR modified the inverse association between long-term statin use and risk of CRC. Genotyping for all SNPs in HMGCR was successful for 1,780 cases and 1,863 controls with complete data on long-term statin exposure. No departure from Hardy-Weinberg equilibrium in the allele frequencies among controls was observed. Although the six HMGCR SNPs were not significantly associated with CRC after corrections for multiple comparisons (as noted above), one of these SNPs, rs5908, showed suggestive evidence of an association before the corrections. The A/G allele was observed in 12 cases and 28 controls compared with the A/A genotype in 1,768 cases and 1,835 controls, and no G/G heterozygotes were observed (heterozygote OR, 0.44; 95% CI, 0.23-0.88; P = 0.015). However, this association was not significant after adjustment for multiple comparisons.

As previously reported, long-term use of statins was associated with a significantly reduced relative risk of CRC (OR, 0.50; 95% CI, 0.40-0.63; ref. 21). Simvastatin and pravastatin accounted for the overwhelming majority of statin prescriptions among users. Our pharmacogenetic analysis showed that the protective association was significantly stronger among individuals with the A/A genotype.
for rs12654264 than among those with the T/T genotype, with A/T heterozygotes experiencing intermediate relative risk (Fig. 1; Supplementary Table S1). The case-only analysis provided a test for interaction that was significant even after Bonferroni correction ($P = 0.0012$; Supplementary Table S2). Similar trends were noted for other SNPs within the statin binding domain of HMGCR that are in linkage disequilibrium with rs12654264. To consider these associations in further detail, haplotype analysis showed that two haplotypes of $HMGCR$ significantly modified the association between long-term statin use and risk of CRC (Table 2). These results were noteworthy because they recapitulated the published experience of statin pharmacogenetics for lipid therapy. Analyses adjusted for age, gender, and ethnicity were essentially unchanged from unadjusted analyses, and adjusted analyses are reported in Table 2. These results support our hypothesis that this type of pharmacogenetic variation might also apply to the chemopreventive potential of statins but is not a CRC risk factor by itself.

We then considered why the relationship between $HMGCR$ genotype and the strength of protection by statins might be captured by rs12654264. This particular variant is a noncoding SNP located in intron 12 of $HMGCR$ IVS 12. The COOH terminus of HMGCR contains the binding site for statins. Previously, a common alternative spliced form of HMGCR (HMGCR v1) has been described that does not include exon 13, which encodes part of the statin binding domain. The HMGCR v1 transcript has decreased binding affinity for statins (11, 28). One $HMGCR$ SNP in IVS 13 (rs3846662) has been described that affects the relative ratios of the full-length HMGCR and alternatively spliced HMGCR v1 transcripts. Because rs3846662 is in high linkage disequilibrium ($r^2 = 0.84$) with rs12654264, we performed mechanistic studies of HMGCR alternative splicing in CRC cell lines, postulating that the modification of statin efficacy that we observed with rs12654264 is due to alternative splicing. First, we tested whether we could detect HMGCR v1 transcripts in colon cancer cell lines. Using reverse transcription-PCR, we were able to detect HMGCR v1 splicing in all cell lines tested (data not shown).

To understand molecular mechanisms of action and test the hypothesis that rs12654264 denotes a haplotype that affects $HMGCR$ cholesterol synthesis and alternative splicing, we studied CRC cell lines with all three genotypes of rs12654264 by culturing cells with atorvastatin. Statins reduced cholesterol synthesis in CRC cell lines with the A/A genotype significantly more than in cell lines with the T allele (Fig. 2).

To understand whether alternative splicing could be a mechanism of rs12654264 accounting for this genotype-specific inhibition of cholesterol synthesis, we assayed

**Table 2.** Association between $HMGCR$ haplotypes and statin use among cases, adjusted for age, gender, and ethnicity

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>OR (95% CI)</th>
<th>Log-additive $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAACAA*</td>
<td>1.00†</td>
<td></td>
</tr>
<tr>
<td>CTATAA</td>
<td>1.79 (1.25-2.58)</td>
<td>0.0017</td>
</tr>
<tr>
<td>TTACAA</td>
<td>1.65 (1.12-2.43)</td>
<td>0.011</td>
</tr>
<tr>
<td>CTACAA</td>
<td>1.40 (0.86-2.26)</td>
<td>0.17</td>
</tr>
<tr>
<td>Rare</td>
<td>0.69 (0.22-2.33)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Haplotypes defined by rs10515198, rs12654264, rs2241402, rs2303152, rs4704209, and rs5908, respectively. †Reference haplotype.
ratios of full-length HMGCR and HMGCR v1 transcripts using TaqMan in colorectal cell lines. The rs12654264 A allele designates the full-length mRNA isoform. When measured as a ratio of HMGCR v1/HMGCR, carriers of the A allele have a lower ratio compared with carriers of the T allele (Fig. 2). The difference between the ratios of rs12654264 homozygous (AA versus TT) full-length HMGCR and HMGCR v1 transcripts is statistically significant ($P < 0.03$). The difference between the ratios of each transcript between cells carrying each homozygous genotype and the lines carrying the heterozygous genotypes is not statistically significant. These data are consistent with our hypothesis that this variant affects alternative splicing of HMGCR. Carriers of the A allele express more of the full-length isoform that binds statins. Therefore, carriers of the A allele are more sensitive to statins and are more likely to experience the risk reduction associated with long-term use. Carriers of the T allele are less sensitive to statins, apparently because they express more of the HMGCR v1 isoform that is missing exon 12 at the statin-binding site. Also consistent with our epidemiologic observation, rs12654264 is not strongly associated with altered overall HMGCR mRNA expression levels when tested in CRC cell lines and in 296 primary CRCs from our study population (data not shown). We conclude that genetic variation in HMGCR makes a profound difference to the risk of CRC in the presence of statins, but contributes little when considered in non–statin users.

The SNP rs12654264 now also has been found to be associated with serum cholesterol in at least two independent studies (29, 30). To understand the role of rs12654264 in the modulation of cholesterol levels in our study, we compared serum cholesterol levels between rs12654264 carriers and noncarriers (Table 3). We used data from all available cases and controls, regardless of whether the cholesterol level was drawn before or after diagnosis or interview. To ensure the representativeness of this larger sample set, we compared prediagnostic and postdiagnostic cholesterol levels in cases and preinterview and postinterview levels in controls, and no meaningful differences were found. Consistent with the two previous studies of cardiovascular disease (29, 30), carriers of at
least one copy of the rs12654264 T allele in our study population had statistically significant higher serum LDL and total cholesterol levels (t-test P = 0.011 and P = 0.049, respectively).

Discussion

This study identified an HMGCR genetic variant that significantly modifies the relationship between long-term use of statins and reduced risk of CRC. This variant had no significant effect on CRC risk in non–statin users. After we began this study, rs12654264 was found to be associated with higher serum circulating cholesterol in at least two independent cohorts being studied for the genetics of cardiovascular disease (29, 30). In our study group, rs12654264 carriers had a statistically significant higher serum cholesterol level (Table 3). Together, these studies provide strong evidence that rs12654264 plays an important role in the modulation of HMGCR activity for reducing both cholesterol levels and CRC risk.

Only one common alternatively spliced isoform of HMGCR, HMGCR v1, has been previously described (11, 28). This isoform deletes exon 13, which encodes part of the statin binding domain of HMGCR. In the CAP study, mRNA expressions of both the full-length transcript and the HMGCR v1 transcript (lacking exon 13) were studied in 170 simvastatin-incubated immortalized lymphocyte cell lines derived from participants who were treated with simvastatin at 40 mg/d for 6 weeks (11, 28). Greater upregulation of HMGCR v1 in vitro correlated significantly with smaller in vivo reductions in plasma levels of total cholesterol and LDL. By siRNA knockdown of the full-length transcript, the authors found that HMGCR enzyme activity in cells enriched in HMGCR v1 was more resistant to statin inhibition, consistent with the association of increased alternative splicing with reduced statin response in the CAP study. In summary, as a result of the coding exon deletion in HMGCR v1, this transcript is less responsive than the full-length HMGCR transcript to statin inhibition of cholesterol synthesis (11).

Consistent with our pharmacogenetic association data and the CAP study, functional studies in CRC cell lines support altered ratios between the full-length HMGCR and the alternatively spliced (HMGCR v1) mRNA isoforms as an important mechanism of differential host sensitivity to statin effects on CRC risk. The rs1265464 A allele and the rs3846662 T allele denote decreased alternative splicing of HMGCR in CRC cells, with concomitantly increased full-length HMGCR isoform. The increase in full-length HMGCR (statin-responsive) transcript versus the exon 13–deleted (statin-insensitive) HMGCR v1 transcript causes greater sensitivity to statin-dependent repression of CRC cell synthesis of cholesterol. The downstream targets affected by increased CRC cholesterol synthesis and the causal variant(s) underlying HMGCR alternative splicing remain unknown and warrant further studies.

Genetic variation in HMGCR affects statin response. Here we show that this variant influenced serum lipid levels in a large population of patients with and without CRC, consistent with the published literature on the pharmacogenetics of statins. Of significance, this genetic variation may also explain differential sensitivity to statins as chemopreventive agents for CRC. Although the statin-associated reduced risk of CRC is evident among all genotypes, it was greater among individuals carrying two copies of the A allele (versus two copies of the T allele).

Observational case-control studies are subject to the known biases and limitations of retrospective observational data. The limitations of case-control studies, however, are unlikely to influence tests of a priori hypotheses on interactions. Because we show that the genotypes of interest are independent of exposure among controls, the case-only analyses we conducted provided a powerful, valid approach for detecting gene-environment interactions. Furthermore, we have shown that these alleles are closely linked to the expression of different isoforms of HMGCR and that the full-length isoform seen with the A allele leads to a greater reduction of cholesterol by statins. These experimental data match the epidemiologic observations of a correlation between statin sensitivity and HMGCR genotype and offer potential insight into the significance

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Genotype</th>
<th>n</th>
<th>Mean (SE)</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>AA</td>
<td>738</td>
<td>119.51 (1.194)</td>
<td>—</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>1,059</td>
<td>123.38 (1.016)</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>443</td>
<td>122.91 (1.546)</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>AA</td>
<td>738</td>
<td>49.7 (0.455)</td>
<td>—</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>1,058</td>
<td>49.6 (0.385)</td>
<td>−0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>443</td>
<td>49.4 (0.593)</td>
<td>−0.29</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>AA</td>
<td>738</td>
<td>202 (1.526)</td>
<td>—</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>1,059</td>
<td>206 (1.214)</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>443</td>
<td>205 (1.832)</td>
<td>2.7</td>
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</table>

NOTE: P value from global ANOVA of three genotypes. Comparisons for the presence of any T-allele are given in the text.
of these epidemiologic findings for individuals at risk of CRC. We anticipate that genotyping for \textit{HMGCR} rs1265464 may help identify the subset of individuals who are most likely to achieve a CRC risk reduction and cholesterol lowering with statins. The relationship of \textit{HMGCR} rs1265464 with CRC risk may partially explain the variability seen in different retrospective studies of statins and risk of CRC because allele frequencies differ among populations.

Given that approximately 25 million people use statins worldwide, the pharmacogenetics of \textit{HMGCR} could help in developing a more precise, personalized, and cost-effective cardiovascular and cancer risk reduction that targets the individuals who will benefit most and thus minimizes toxicity for those who would benefit least.

References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

National Cancer Institute grants N01-CN43308 (S.M. Lipkin) and R01 CA84188 (S.B. Gruber), University of Michigan Cancer Center Support Grant S 5 P30 CA4592, Spanish Secretaria de Estado de Universidades e Investigacion grant PR2008-0824 (V. Moreno), and the Irving Weinstein and Ravitz Foundation (S.B. Gruber).

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Received 01/20/2010; accepted 02/25/2010; published OnlineFirst 04/19/2010.
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