The melanocortin-1 receptor (MC1R) gene is a key determinant of the physiological variation in human skin pigmentation. It is highly polymorphic, and specific MC1R allelic variants have been shown to be low-penetrance melanoma susceptibility alleles. We investigated the contribution of the MC1R genotype to the risk of sporadic cutaneous melanoma in a population in central Italy. One hundred patients with sporadic cutaneous melanoma of any stage and 100 unrelated control individuals were consecutively recruited between 1 September 2000 and 31 December 2001. Information on ethnic background and residential history, phenotypic risk factors for melanoma and ultraviolet exposure habits was collected through a standardized questionnaire and total skin examination. Sequence analysis of the entire coding region of the MC1R gene was performed. A total of 26 MC1R variants, including a novel 123_124insT allele, was identified in our population, with the most frequent allele being V60L. Carriers of high-penetrance R' MC1R alleles, that define MC1R variants strongly associated with the red hair colour phenotype, showed a statistically significant increase in melanoma risk [odds ratio (OR), 2.55; 95% confidence interval (CI), 1.19-5.55]. No significant association with melanoma risk was observed for
carriers of 'r' variants (OR, 0.90; 95% CI, 0.45-1.82). Amongst individual MC1R variants, the R151C allele was significantly associated with melanoma, with an OR of 2.94 (95% CI, 1.04-8.31). After stratification for clinical and ultraviolet exposure risk factors, the melanoma risk associated with high-penetrance 'R' variants appeared to increase significantly, mainly in the presence of clinically atypical naevi, more than 50 melanocytic naevi, high recreational sun exposure and occupational sun exposure. These results support the contribution of high-penetrance MC1R variant alleles to genetic predisposition to sporadic cutaneous melanoma in a population in central Italy.