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Letters to the Editor

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To the editor: Although the existence of the CpG island methylator phenotype (CIMP) in colorectal cancer may be controversial, we were disappointed that the review by Agrawal *et al* of DNA methylation in breast and colorectal cancer[1] did not cite recent studies that support CIMP. Although all studies of colon cancer have not reported the same associations with CIMP, there has been remarkable unanimity with respect to a very strong relationship with the *BRAF* V600E mutation. This relationship is independent of microsatellite instability and has been observed using different techniques and CpG islands to evaluate CIMP.[2–4] Also, a significant relationship between CIMP and cigarette smoking independent of microsatellite instability has been seen;[5] this relationship to an epidemiologic risk factor also supports CIMP as a true phenotype.

With regard to hereditary nonpolyposis colorectal cancer (HNPCC), it is somewhat misleading to state that ' … aberrant methylation of the mismatch repair genes, … hMLH1 or hMLH2, are the basis for the cancer (*in hereditary non-polyposis colorectal cancer*).' The overwhelming percentage of cases of HNPCC is the result of a germ-line mutation and a subsequent somatic second hit (usually mutation) in one of the mismatch repair genes; germ-line methylation is an extremely rare cause of this syndrome.

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In reply: We thank Dr Samowitz and Dr Ogino for their letter in response to our paper on DNA methylation in breast and colorectal cancer.[1] Colorectal cancers can evolve through multiple pathways that are primarily defined on the basis of microsatellite instability and CIMP status.[2] In our article, we briefly discussed the potential role of CIMP in the diagnosis of colorectal cancer. Based on the published reports cited in our article, there is still controversy on the association of CIMP with colorectal cancer. Since the publication of our article, we have come across the published reports of Dr Ogino and co-workers on molecular features of CIMP tumors, suggesting the classification of colorectal cancers into three subgroups based on CIMP status: Non-CIMP, CIMP-low, and CIMP-high.[3] In our article, we had mentioned about the CIMP(+) and CIMP(−) colorectal tumors. However, to the best of our knowledge, there is no strong evidence to support the existence of CIMP-low. Furthermore, the origin of CIMP-low tumors is not known. It is our understanding that only a subgroup of colorectal cancers, CIMP-high, show a correlation with *BRAF* V600E mutation, suggesting that CIMP-high colorectal cancers might originate from serrated polyps. But, there could be both microsatellite instable-CIMP+ and microsatellite stable-CIMP+ subsets of colorectal cancer. We do not disagree with Dr Samowitz and Dr Ogino that CIMP could be a true phenotype of a subset of colorectal cancers. Thus, there are clearly distinct subclasses of colorectal tumors based on molecular heterogeneity. Many recent reports support this view.[3–4] Nonetheless, as pointed out in a recent commentary, there are more questions than the answers in this complex area of CIMP and colon cancer.[5]

We are also aware of the association between the exposure to epimutagens, including tobacco smoke,