NOD2 and Colorectal Cancer: Guilt by Non-Association

To the Editor: In a recent issue of Cancer Research, Kurzawski et al. (1) describe a potential association between the 3020insC NOD2 single nucleotide polymorphism (SNP13) and the risk of colorectal cancer. They based their study on the following concept: first, the 3020insC NOD2 polymorphism is associated with a higher susceptibility to Crohn’s disease; and second, Crohn’s disease is associated with a higher risk of colorectal cancer. Is it even warranted that such an association would be predicted to exist? We do not believe so.

Crohn’s disease is not a single disease but rather a common denominator for different chronic inflammatory diseases of the intestine. Historically, colonic Crohn’s disease has not been distinguished from ulcerative colitis. About 30 years ago, the first reports described a diverse natural history for colonic Crohn’s disease and ileal Crohn’s disease (2). This first attempt to discriminate between various subgroups of Crohn’s patients led to a proposal for a phenotypic classification (3), which was taken up, further developed, and evaluated by an international working group (4). According to the Vienna Classification, Crohn’s disease can be separated by three categories: age at diagnosis, disease location, and disease behavior. The more recent identification of NOD2 polymorphisms as genetic risk factors for the development of Crohn’s disease serves as proof of principle: several studies showed unequivocally that NOD2 variants confer susceptibility to ileal Crohn’s disease but not colonic Crohn’s disease (5, 6). Furthermore, NOD2 polymorphisms are not associated with ulcerative colitis or indeterminate colitis, two distinct colonic forms of inflammatory bowel diseases (6).

Higher risk for development of colorectal cancer in inflammatory bowel disease has been recognized primarily for ulcerative colitis. About 30 years ago, the first reports described a diverse natural history for colonic Crohn’s disease and ileal Crohn’s disease (2). This first attempt to discriminate between various subgroups of Crohn’s patients led to a proposal for a phenotypic classification (3), which was taken up, further developed, and evaluated by an international working group (4). According to the Vienna Classification, Crohn’s disease can be separated by three categories: age at diagnosis, disease location, and disease behavior. The more recent identification of NOD2 polymorphisms as genetic risk factors for the development of Crohn’s disease serves as proof of principle: several studies showed unequivocally that NOD2 variants confer susceptibility to ileal Crohn’s disease but not colonic Crohn’s disease (5, 6). Furthermore, NOD2 polymorphisms are not associated with ulcerative colitis or indeterminate colitis, two distinct colonic forms of inflammatory bowel diseases (6).

If the authors studied the proper population of interest (i.e., inflammatory bowel disease-related colorectal cancer) with appropriate age- and ethnicity-matched controls, did not split cases into arbitrary age groups, performed corrections for multiple testing, and assessed a gene dose relationship, they would have most likely come to different conclusions. We are highlighting this because we believe that it is incorrect to spread the misconception that this NOD2 variant is associated with colorectal cancer, particularly with regard to the consequences for genetic testing and genetic counseling.

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In Response: We read with interest the comments by Gasche and Carethers and have some comments on their interpretation of our report (1).

Gasche and Carethers base criticisms of our results on two assumptions: first, we based our study on the finding that the 3020insC NOD2 polymorphism is associated with a higher susceptibility to Crohn’s disease; and second, that Crohn’s disease is associated with a higher risk of colorectal cancer. There are numerous reports of Crohn’s disease being linked to an increased risk of colorectal cancer development (2–6). The evidence, however, is controversial because other studies have not been able to identify any association with colorectal cancer risk (7–10). One of the confounding factors that has resulted in this apparent dichotomy, the treatment of patients with Crohn’s disease with 5-aminosalicylic acid and/or colectomy for disease control, was identified in a recent Danish study (11). Gasche and Carethers are emphasizing that NOD2 variants confer susceptibility only to ileal Crohn’s disease and not to colonic Crohn’s disease. Actually, according to the Vienna Classification, there are four subtypes of Crohn’s disease, depending on the location where the colon is involved in L2 colonic and L3 ileocolonic subtypes. Almost all of the reports show that NOD2 variants are not associated with L2 but are associated with L1 ileal and L3 subtypes (Table 3 in Ref. 12).

What we were primarily interested in was the relationship between the inactivating 3020insC NOD2 polymorphism and cancer risk, which has not, to the best of our knowledge, been examined previously. Furthermore, we did not select for inflammatory bowel disease patients because we used an unselected consecutive series of colorectal cancer patients, irrespective of any other co-morbidities. Finally, not all patients with inflammatory bowel disease develop cancer, suggesting that there are either environmental influences affecting malignant disease expression, genetic differences, or both. Our assumption was that it was more likely to be a mixture of both environmental and genetic factors that changed malignant disease risk, and as such, an excellent candidate gene was NOD2.

In summary, we do not believe that the criticisms put forward by Gasche and Carethers address the issues in which we were primarily interested. The results of our study indicate that the 3020insC NOD2 polymorphism is associated with an increased risk of colorectal cancer, which is in keeping with the notion that inflammatory responses are critical in ameliorating environmental stress.

References

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