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PROCEEDINGS

Gut health, genetics and personalised nutrition

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Diseases of the alimentary tract are major sources of morbidity and mortality across the globe. The gut is particularly prone to cancers, many of which show striking geographical variations in incidence. For example, colorectal cancer is one of the three most common causes of death from cancer in industrialised western countries, but it is strikingly rare in the less developed world. That this is due primarily to environmental rather than genetic factors is clear from the fact that the age-adjusted risk of colorectal cancer rises inexorably as industrialisation and prosperity increase, and the fact that migrants from countries with a low incidence rapidly acquire the disease incidence typical of the population that they join. It is estimated that around 80% of sporadic colorectal cancer is caused by environmental factors, which remain poorly understood. Amongst these, diet and physical activity seem to be particularly important.

Within populations at high risk of colorectal cancer, the lifetime risk of developing the disease is currently around 5–6%, and genetic factors are thought to play an important role in shaping individual vulnerability. Only about 3% of sporadic colorectal cancer in western countries is caused by known genetic syndromes such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Nevertheless, individuals with a familial history of colorectal cancer show a substantial increase in risk of the sporadic disease compared to those with no family history. This indicates that low-penetrance genes are involved in the disease process, so that individual risk is shaped by a combination of environmental and genetic factors [1]. In view of the strong effects of diet on colorectal cancer, it is probable that many of the genetic variations that influence an individual's risk do so by modulating the effects of environmental factors, including both the adverse and protective effects of diet and metabolic status. Genetic epidemiology, in which the effects of interactions between genes and the environment are investigated, provides the means to explore this issue.

One increasingly important approach to the analysis of interactions between genetic and environmental factors is the use of Mendelian randomization in the design of epidemiological studies. This approach avoids the bias and potential confounding effects inherent in many conventional investigations of the relationship between disease and environmental exposures by exploiting the principle that individual alleles are randomly assorted from parents to offspring [2]. Recent studies on the possible role of insulin-like growth factor (IGF)-1 as a causal factor linking body-mass and energy balance to colorectal carcinogenesis provide on example of this approach. IGF-1 is a pro-mitotic, anti-apoptotic peptide that occurs at relatively high levels in the plasma of individuals with a high BMI and relatively low physical activity. The hypothesis to be tested is that IGF-1 is one many endocrine factors associated with Western diet and lifestyle, that can act on the intestinal mucosa in such a way as to increase its vulnerability to neoplasia. For example, mucosal field changes, in which the ratio of mitosis to apoptosis in colorectal crypts is increased, might favour the retention of precancerous cells.

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Evidence to support the involvement of IGF-1 in colorectal carcinogenesis comes from five cohort studies reviewed in the meta analysis of Renehan et al. [3], showing an increased risk of colorectal cancer in individuals with relatively high levels of IGF-1 (odds ratio 1.58; 95% confidence interval 1.11–2.27). A recent study by Morimoto et al. [4] examined the relationship between two common polymorphisms affecting IGF-1, a cytosineadenosine repeat in *IGF-1*, and a G–C single nucleotide polymorphism in the gene coding for IGF binding protein (*IGFBP-3*). Statistically significant relationships between some of these polymorphisms and the relationship between BMI and risk of colorectal cancer were observed, and the authors concluded that their findings provide moderate support for the involvement of IGF-1 in the aetiology of colorectal cancer.

Although the adverse metabolic effects of over-consumption of energy and lack of physical exercise are emerging as key drivers for the high incidence of colorectal cancer seen in western industrialised societies, there is also clear evidence of protective effects associated with high consumption of certain specific food components, including dietary fibre, fruits and vegetables, and certain micronutrients such as folate and vitamin D. Mendelian randomisation also provides a powerful method of exploring the molecular mechanisms involved in these protective effects. One example of this approach is provided by the study of London et al. [5] who showed that the protective effects of brassica vegetables against lung cancer in a Chinese population depended on the genetic status of individuals with respect to genes coding for various subfamilies of the Phase II enzyme glutathione*S*-transferase. The protective effect appears to be strongest in individuals who are null for *GSTT1* and *GSTM1*, and this relationship has recently been confirmed in a European study [6]. A similar protective effect of broccoli against colorectal adenomas has been reported for subjects who are null for *GSTM1* [7]. If these relationships are confirmed it may mean that dietary advice needs to be targeted on individuals with a particular genetic profile. However the possibility that in the future, large-scale genetic profiling of the population might be put in place in order to achieve such targeting raises considerable economic and ethical problems that will need to be addressed by society as a whole.

In conclusion, there is strong evidence that colorectal cancer, and the less common but rapidly advancing disease, adenocarcinoma of the oesophagus, are linked to the adverse metabolic effects associated with western lifestyles. However, within populations at high risk, there is also clear evidence that specific dietary components exert protective effects. The extent to which these various environmental factors contribute to an individual's risk of disease depends upon their genetic background. To fully understand these aspects of individual risk we must identify a host of low-penetrance genes that shape our interactions with the environment. Molecular epidemiology, in which groups of individuals are stratified according to well-defined genetic criteria, can contribute greatly to our understanding of these disease mechanisms. In the future, a greater understanding of the role of low-penetrance genes in colorectal cancer and other diseases of the gut, coupled with genetic screening for common polymorphisms, and perhaps epigenetic analysis of selected CpGislands, is likely to lead to new, genetically-tailored preventive strategies that can be applied to individuals [8]. However the extent to which such personalised preventive nutrition becomes available to the general population, as opposed to individuals who have sought medical advice because of a strong family-history of disease, remains to be seen.

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