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Involvement of genetic factors and lifestyle on the occurrence of colorectal and gastric cancer

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ABSTRACT

Gastrointestinal cancers are diseases due to genetic and environmental factors. In this present work we are interested in the influence of environmental factors on the occurrence of gastrointestinal cancers in Tunisian population. We found that the MTHFR C677T polymorphism was associated with colorectal cancer ($P < 0.04$) but not with gastric cancer. In addition, we have shown that alcohol is associated with an increased risk of colorectal cancer, but the consumption of cheese is protective. Furthermore, we studied tymidylate synthase gene involved in folate metabolism. Indeed, we observed that the 5′UTR repeat polymorphism, is associated with risk of colorectal cancer, and the LL genotype (3R/3R) was significantly frequent in patients with colorectal cancer compared to controls ($p = 0.002$; OR = 2.7, 95% CI = 1.4–5.2). While we found that SL genotype (2R/3R) was associated with risk of gastric cancer ($p = 0.015$; OR = 4.46, 95% CI = 1.08–19–64). This polymorphism was also shown to be a predictor of response to chemotherapy based 5′-fluorouracil.

However, we are interested in studying the GPX −1 gene involved in phase I metabolism of xenobiotics. We therefore evaluated the risk of TT genotype in GPX-1 C599T polymorphism with the onset of gastric cancer ($P = 0.0001$; OR = 5.41, 95% CI 1.98 to 15.58) and colorectal cancer ($P = 0.00008$; OR = 4.40, 95% CI 1.93 to 10.27). To clarify the possible relationship between environmental factors and the occurrence of the disease, we studied the additive effect of risk genotype and behavior in order to highlight the interaction of gene-environment factors.

Abbreviations: GIC, GIC gastro-intestinal cancer; GC, gastric cancer; CRC, colorectal cancer; ROS, reactive oxygen species; ABTS, 2,2′-azino-3-ethylbenzothiazoline-6-sulfonic; EAO, activated oxygen species; VNTR, variable number tandem repeat; SNP, single nucleotide polymorphism; GPX, glutathione peroxydase; GSH, glutathione; MTHFR, methylenetetrahydrofolate reductase; TS, thymidylate synthase; GSSG, glutathione redctase.

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1. Introduction

Gastrointestinal cancer remains the focus of numerous epidemiological and therapeutic studies; it is well-known for decades to be a major public health problem and a cause of mortality and morbidity worldwide.

One of the characteristic features of cancer is the growth of cells whose morphology and behavior are abnormal. They often end up forming a malignant tumor that tends to spread through the bloodstream or through the lymphatic system.

In normal tissue, cell cycle includes four phases: cells do not divide in the G0 phase.

- In the G1 stage, the cells are preparing to enter the S phase by synthesizing proteins required for DNA synthesis.
- During the stadium G2, cells prepare the M phase of the synthesis of proteins required for cell division.
- The phase M includes cell division into two identical cells; therefore, it is the mitosis stage. Different mechanisms allow the regulation of the cycle cell by acting on the transition between the phases or on very precise control points. A fault in a control system will cause an uncontrolled multiplication which together with the exhaust to apoptosis creates immortal cell. Carcinogenesis has three essential phases:

1.1. The initiation step

The initiation step begins when carcinogenic chemicals bind to deoxyribonucleic acid (DNA). Lesions may also occur under the effect of ionizing radiation or ultraviolet radiation. In this case, the activated oxygen species (ROS), which include free radicals and singlet oxygen, play an important role in the alteration of genetic material of cells.

The hydroxyl radical attacks the guanine purine base of DNA, which is transformed into 8-hydroxy-2′deoxyguanosine. This metamorphosis results in the occurrence of a mutation at the DNA level. The singlet oxygen reacts with guanine to form another oxide derivative, 8-oxo-7, 8-dihydroguanine.

ROS can also act as secondary messengers in the cell by modifying the redox regulation of glutathione (GSH) which is an important antioxidant. Therefore, it induces in an activation of thioredoxin (TRX) which stimulates the transcription factor NF-kB. Once induced, the NF-kB migrates into the nucleus of the cell where it can transactivate target genes and participates in the synthesis of many mediators such as adhesion proteins involved in the process of cancer development.

1.2. Promotion

Promotion is a process that lasts for several years during which the initiated cell is transformed into a pre-neoplastic cell. The promotion may occur spontaneously or be induced by a tumor promoter such as dietary lipids, hormones or even inflammation (an important source of EOA production).

These factors will allow the maintenance of the immortal character of each cell during its multiplication. Pre-neoplastic cells have a modified external appearance; therefore, theylose their original function, and are differentiated by adopting new properties.

1.3. Progression

Progression is a phase during which the pre-neoplastic cells progress to neoplastic or cancerous cells. It corresponds to a runaway tumor process due to the inability of the immune system to recognize cancer cells as abnormal, persistence of the causal factor or disturbances in the defense mechanisms (DNA repair systems to, for example, excision of oxidized bases) induced an increase in oxidative stress. Once formed, malignant tumors which consist of a large number of cells can invade nearby tissues or reach other organs, and then form secondary tumors called metastases.

In this study, we focus specifically on gatro-intestinal cancers. Most colorectal cancers are sporadic; thus they occur in individuals with no personal or family history of first degree, as opposed to the hereditary form that occurs in the case of two rare autosomal dominant disorders include HNPCC Lynch syndrome (hereditary non for polyposis colorectal cancer). The familial form is inherited as an autosomal dominant; it is hardly distinguishable sporadic forms, which form is a constitutional mutation of a gene belonging to the MMR family that encodes proteins ensuring the repair of DNA. This type of mutation causes a high risk of developing colorectal cancer. However, gastric cancer is a very serious cancer with a poor prognosis which has a main sporadic and very rare inherited form. The genesis of sporadic gastrointestinal cancers involves genetic, environmental, and nutritional factors. Thus, cancer is considered as a multifactorial chronic disease involving many genetic, hormonal and environmental factors that can contribute to its growth by acting on the diverse phases of carcinogenesis.

2. Diet, lifestyle and gastro-intestinal cancer

Although, the effect of some environmental factors acts a protective and preventive way, others factors will be a promising tumor growth. In case–control studies, the possible association between individual dietary items, environmental factors, level of education, occupation, and drinking beverages on gastrointestinal cancers has been evaluated. The frequency of food consumption and other factors were recorded before diagnosis of these cancers.

According to consumption of tobacco, smokers are characterized by an average number of cigarettes smoked per day. In many prospective studies a significant increase of cancer risk was associated with the use of tobacco.

Folate is necessary for generating a new cell (Kamen, 1997) considering its implication in DNA synthesis, methylation and repair. Thus, some nutrients involved in folate metabolism such (Vitamin B12, methionine...) and alcohol intake has an effect on folate level and on cancer risk. It has been reported in some studies that alcohol intake influences metabolism of folate by reducing folate absorption and inhibiting methylation and deactivating methionine synthase (Mason and Choi, 2005). Moreover, alcohol intake may modify the inverse association between folate intake and plasma homocysteine level (Chiuve et al., 2005). The risk of alcohol intake was indeed shown for gastric cancer.

Consumption of derivatives of milk such as butter, yogurt and cheese was not one of the causes of gastrointestinal cancers. Frequent consumption of milk —more than three times per week- is protective against colorectal cancer however no effect of yogurt and cheese was shown. Several epidemiologic studies examined the interaction between dairy product and gastro-intestinal cancer but their findings have been inconclusive. Dairy products contain also Vitamin B12, or cobalamin. Milk is an essential source of Vitamin B12 and interferes with folate metabolism. A meta-analysis of 10 cohort studies (more than 500,000 patients followed for 6–16 years, 4992 colorectal cancers), published in 2004 shows that the consumption of milk (and calcium) is associated with a decrease of approximately 15% risk of colorectal cancer, the analysis suggests a threshold effect at about 1000 mg/day of calcium (Cho et al., 2004). Since then, four large cohort studies, including a French study (E3N Group et al., 2005; Park et al., 2007) confirm the protective effect of dairy products against the risk of adenoma or cancer, in both men and women, with a decrease risk of 15–50% depending on the study. The effect is mainly due to calcium: for example,