A Study of the Prognostic Value of Protein COX-٢ in Colorectal Carcinoma

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دراسة القيمة التنبؤية لبروتين كوكس-٢ فى سرطان القولون والمستقيم

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List of Abbreviations

ACF	Aberrant Crypt Foci
APC	Adenomatous polyposis coli
CEA	Carcinoembryonic Antigen
COX	Cyclooxygenase
COX -١	Cyclooxygenase-١
COX -٢	Cyclooxygenase-٢
COX -٣	Cyclooxygenase-٣
CRC	Colorectal carcinoma
DCC	Deleted in Colon Cancer
FAP	Familial Adenomatous Polyposis
hCG	human Chorionic Gonadotropin
HIF١	Hypoxia-inducible factor-١
HNPCC	Herediatry Non polyposis Colorectal Cancer
IL-١beta	Interleukin-١beta
IL-٦	Interleukin-٦
MMP	Matrix-Metalloproteinase
MMR	Mismatch Repair
MSI	Microsatellite instability
MSS	Microsatellite Stable
NO	Nitric Oxide
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PGs	Prostaglandins
TxA٢	Thromboxane A٢
VEGF	Vascular endothelial growth factor

Introduction

Colorectal cancer is the third leading cause of cancer death in Western Countries. Between ٢٠٪ and ٥٠٪ of patients with colorectal cancer will probably die within five years of diagnosis as the result of extensive disease metastasis. In the United States, colorectal cancer affects nearly ١٥٠,٠٠٠ people each year, with as many as ٥٦,٧٣٠ deaths anticipated in ٢٠٠٤ ***(Hawk et al., ٢٠٠٤)***.

In Egypt, colorectal cancers constituted ٥,٠٥٪ of total malignancies in the period from ١٩٨٥ to ١٩٨٩ in National Cancer Institute ***(Mokhtar, ١٩٩١)***. Colorectal cancer constituted ٤,٣٪ of total malignancies in National Cancer Institute during the years ٢٠٠٣ and ٢٠٠٤ ***(Mokhtar et al., ٢٠٠٧)***.

In Gharbiah, Colorectal Cancer constituted ٣,٨٪ of total cancers during the year ١٩٩٩ ***(Ibrahim et al., ٢٠٠٢)***. And Colorectal cancer constituted ٤,١٪ of total cancers , ٣,٦٪ of total cancers in males and ٤,٥٪ of total cancers of females during the period form ٢٠٠٠ to ٢٠٠٢ ***(Ibrahim et al., ٢٠٠٧)***.

Because of its aggressiveness as a fatal disease, many studies were done to assess the prognostic factors of colorectal cancer; one of these factors is COX-٢ (Cyclooxygenase-٢).

Cyclooxygenase (COX) is a key regulator enzyme in the synthesis of prostaglandins (PGs). The two iso enzymes of COX, termed Cyclooxygenase-١ (COX-١) and Cyclooxygenase-٢ (COX-٢), have been identified. COX-١ is constitutively expressed in virtually all tissues and regulates normal physiological functions ***(Wiese et al., ٢٠٠١)***.

COX-٢ is the best defined molecular target of NSAIDs (non-steroidal anti-inflammatory drugs) and regulates the synthesis of prostaglandins (PGs), COX-٢ (also known as prostaglandin H synthase-١) is upregulated in response to inflammatory cytokines, growth factors and tumor promoters ***(Thun et al., ٢٠٠٢)***.

COX-٢ overexpression in other epithelial cancers including pancreas ***(Tucker et al., ١٩٩٩)***, esophagus ***(Shamma A et al., ٢٠٠٠)***, breast ***(Ristimaki A et al., ٢٠٠٢)*****,** stomach ***(Van Rees et al., ٢٠٠٢)*** and lung ***(Altorki et al., ٢٠٠٣)***, **is** also found primarily in the malignant epithelial cells.

Potential mechanisms by which COX-٢ may contribute to tumorigenesis including promoting cell division ***(Fosslien, ٢٠٠٠)***, increased cell invasiveness ***(Reddy et al., ٢٠٠٢),*** alternating cell adhesion and enhancing metastasis ***(Chen et al., ٢٠٠١)***, inhibiting apoptosis ***(Nzeako et al., ٢٠٠٢)*** and stimulation of angiogenesis ***(Leahy et al., ٢٠٠٠ and Rao et al., ٢٠٠٤)***.

COX-٢ expression is gradually up regulated in the development from normal epithelium to adenomas and from early colorectal cancers to advanced colorectal cancers, so COX-٢ expression can be regarded as independent risk factor of poor prognosis for postoperative patients with advanced colorectal cancers ***(Zhan et al., ٢٠٠٤)***.

Finally COX-٢ overexpression may confer prognostic information in human colorectal cancers, as its overexpression in primary tumors was associated with more advanced tumor stage, increased tumor size and positive lymph node status ***(Zhang and Sun, ٢٠٠٢)***.

Aim of the Work

The aim of this work is to study COX-٢ expression in colorectal carcinoma and its value as a prognostic factor in colorectal carcinoma.

Conclusion and Recommendation

From this study, we conclude that strong positive COX-٢ expression was correlated with the most important prognostic parameters including, tumor stage, depth of invasion as well as lymph nodes metastasis; and this relation was statistically significant. So, positive COX-٢ expression might predict tumors with more aggressive behavior. Thus COX-٢ expression maybe useful in selection of patients of CRC at high risk of tumor progression.

We recommend further follow-up studies on COX-٢ expression on large number of cases of CRC to confirm its prognostic value in relation to survival and other effective prognostic factors such as tumor stage, tumor invasion and presence of lymph node metastasis, in order to select CRC patients who would benefit from adjuvant therapeutic management.

Discussion

Colorectal carcinoma is the third most common cancer in the world and the second most common cause of cancer related death ***(Ricchi et al., ٢٠٠٣) (Jemal, ٢٠٠٥)*** . During the year ٢٠٠٠, in the United States, ١٣٠,٢٠٠ new cases of colon cancer and rectal cancer were reported ***(Nelson et al., ٢٠٠١)***. Colorectal cancer affects nearly ١٥٠,٠٠٠ people each year with as many as ٥٦,٧٣٠ deaths anticipated in ٢٠٠٤ ***(Hawk et al., ٢٠٠٤)***. In Japan, ٣٦,٠٠٠ patients died of this cancer in ٢٠٠١ ***(Kotake et al., ٢٠٠٣)***.

In Egypt, the median age is ٦٥ years, but younger (٥٠ years) in cases complicating polyposis and ulcerative colitis. Male predominance is ٢:١ in the rectum and ١,٣:١ in the colon ***(El-Bolkainy et al., ٢٠٠٥)***.

The overall prognosis of colorectal carcinoma remains poor, despite the improving survival of patients with surgically operable tumors, and use of main conventional prognostic factors such as tumor stage, depth of tumor invasion and the presence of lymph node metastasis. So, attempts to find new biologic markers that could identify patients with poor prognosis remain under investigation.

COX-٢ overexpression has been detected in several other carcinomas including the breast cancer ***(Rozic et al., ٢٠٠١)***, in the