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# Studies on Colorectal Cancer in The Kingdom of Saudi Arabia: A Portrait Through Pre and Post-Millennium

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**Abstract:** Literature reports suggest a tremendous decline in the global incidence, mortality and morbidity of Colorectal Cancer (CRC) during the post-millennium as compared to the pre-millennium. These developments are attributed to the advancement in technicalities and researches. The status of CRC in the Kingdom of Saudi Arabia (KSA) during the pre-millennium restricted to most of the etiological, histological and epidemiological researches while progress around the world had already begun studies on molecular level. During the third millennium, there are active genome level researches in addition to the development of the link of MicroRNAs with progression of cancer. Although, research on gene expression began in KSA but its involvement in the discovery of newer compounds is still a vision. Furthermore, the researches in KSA lag behind in the new developed era of MicroRNAs. This review on the development of research activities on CRC has revealed that researches in KSA are slow and late but do not lag behind in the global scientific maneuvers taking place in the third millennium.

**Key words:** CRC, researches, pre-millennium, post-millennium, gene expression, MicroRNAs

## INTRODUCTION

Changes in peoples' diet and lifestyle have resulted in focusing CRC as a disease of global concern. By millennium, there were about 950,000 cases diagnosed and 500,000 deaths recorded worldwide (Lv *et al*., 2006). However, a report of Globocan revealed a total of 727,000 cases, diagnosed and 319,000 deaths (worldwide) in the more developed nations whereas in the less developed regions, the reported cases were 506,000 and deaths were 288,000. These numbers clearly showed an overall decline in the incidence of CRC and related deaths while the discrepancy in the advanced and developing nations is deemed to be related with the more sources to disease in the developed regions.

The decline in the global CRC incidence and mortality is attributed to worldwide development in the technicalities and involvement of more recent researches in the management of CRC. The post millennium era of scientific developments has made it possible to analyze the knowledge about the genome research in regulation of cell proliferation, differentiation, apoptosis and immunity. Researches on expression of genes are used, not only to characterize the CRC but more recently the technology is applied in the discovery of potential biomarkers and therapeutic targets (Maithel *et al*., 2012; Kelley and Venook, 2011; Larsson *et al*., 2011). While CRC carcinogenesis is extensively investigated at molecular level, more recently it has entered the era of microRNAs. The link of MicroRNAs with formation, angiogenesis, metastasis, chemotherapy and resistance of tumors has become one of the focal issues in the epigenetics of cancer. They regulate gene expression, control cellular mechanisms involved in signal pathways and are very useful in diagnosis and treatment of CRC. Though slow and late but KSA do not lag behind in the global scientific maneuvers taking place in the third millennium. The present study is a brief review of the progress achieved through pre and post-millennium in different areas of management of CRC in KSA.

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## MATERIALS AND METHODS

Published studies selected for inclusion in this review were based on the significance of literature search on experimental work undertaken and published from different research institutions of KSA. The task was met up with peer reviewed English language articles published during the pre-millennium and post-millennium era selected from Pub Med, Pub Med Central, Science Direct, Up-to-date, Med Line, Comprehensive databases, Cochrane library and the internet (Google, Yahoo). The strategy of search combined terms that included the title and the keywords.

**Review of literature:** The incidence of CRC in Saudi Arabia was found to be next only to Breast cancer (Ibrahim *et al*., 2008). The researchers further found that the incidence of CRC in Saudi Arabia between 1994 and 2003 was much more as compared to the prevalence of CRC in the USA. A projection model suggested that the incidence of CRC in Saudi Arabia could increase fourfold in both genders by the year 2030. This is definitely a highly pessimistic figure as it appears to be a remote reality in view of the fast developments taking place in modern researches during the third millennium. A survey of literature published during pre and post-millennium revealed independent levels of development in research activities on CRC however, there is no work to date to specifically show the impact of progress during different era which might be related to incidence and mortality of the disease. Hence, it became imperative to undertake the present investigation to review the researches published during pre-millennium era, post-millennium era and conclusion.

**Pre-millennium era:** The pre-millennium era in Saudi Arabia constituted most of the studies on etiological factors, ethnic basis of the disease, comparison of the disease pattern, the male to female ratio, age-wise affliction, the pathology and stages of the disease, relative frequencies of different cancers, onset of the disease, characterization of the tumor, metastasis and recurrence.

The incidence of lower gastrointestinal tract diseases was observed in 288 patients in the Eastern province of the Kingdom of Saudi Arabia between August 1981 and April 1984. Among these cases, ulcerative colitis and colorectal carcinoma were detected in only 11 (4%) and 4 (1.5%) patients, respectively. Comparative analysis of the disease pattern in the series demonstrated some differences from other series from within the Kingdom and also from other countries (Al-Freihi *et al*., 1986). An evaluation of 158 patients with digestive system neoplasm showed that the male to female ratio at cancer sites of the digestive system was 3:1. As compared to the Western countries, younger patients were encountered with advanced cancer. The outcome of the treatment was poor; the results were attributed to the advanced stage at presentation. The high frequency of GIT cancer and in particular the apparently rising incidence rate of colorectal cancer was attributed to dietary habits and the changing lifestyle of the population (Al-Quorain *et al*., 1988).

Between 1975 and 1989, 528 out of 622 patients registered at King Faisal Specialist Hospital Research Center were Saudi. About 321 were male and 207 were female. The average age was 55.3 and 49.6. One hundred and nineteen were <40 years. More patients with proximal lesions were <40 years. Of the young patients 8.3% had small tumors (<4 cm) compared with 24.9% of patients >40. Mucinous and signet ring carcinoma, in addition to nodal involvement was more common in the young. The older patients had more distant metastases (Isbister, 1992). The gastrointestinal malignancies in patients registered with the National Cancer Registry from the Western Region of Saudi Arabia, recorded from January 1994 till December 1997 was analyzed according to ethnic origin, site, age, sex and relative frequencies of various tumors. A total of 1207 out of 1833 (66%) were Saudis and CRC was the most common malignancy prevalent in both the populations (28.5% Saudis and 36% Non-Saudis). The mean age was 58+16 years. The male to female ratio was 1.67:1 and 80% of the patients were above 40 years. The peak of onset for tumors was between 50 and 70 years of age (Al-Radi *et al*., 2000). Four out of five patients underwent major curative restorative colorectal resections and developed perineal recurrence, 2 developed recurrence in the distal ends of previously identified fistulae in ano and 2 developed recurrence at the site of a previously performed hemorrhoidectomy. The fifth patient developed metastasis to a fistula track prior to surgical intervention (Isbister, 2000).

**Post-mllennium era:** While the epidemiological reports continued as the time advanced, the post-millennium era perceived more of the surgical interventions. Reports on preoperative morbidity and mortality, in addition to anastomotic leakage continued to surface. Furthermore, there was an advancement of histopathological profile and stage differentiation besides classification of different types of CRC (signet cell carcinoma, mucinous adenocarcinoma, metastatic papillary carcinoma and squamous cell carcinoma). The origin of CRC was also given importance. Subsequently, more research on the incidence of lesions, status of polyps and the timing of

the stages started to publish. The research activities in this era start to realize the association between tumor phenotype and mismatch repair gene alteration. The researches on incidence of Microsatellite Instability (MSI) and tumor suppressor gene were highlighted. A high prevalence of genetic alteration in P13K/AKT pathway in Saudi cohort was reported. The relationship of KRAS variants with clinico-pathological characteristics in CRC was another important work. High fatty acid synthase over expression was determined to be a potential biomarker and a novel therapeutic target.

Anastomotic leakage following colorectal resection and anastomosis has been proposed as a colorectal surgical indicator. Leak rates after elective surgery vary and tend to be higher as anastomoses become lower. In a study on 1,348 CRC patients between 1990 and 1999, it was shown that inspite of the precautions to see that patients are fit for the surgery, stomata are used liberally and good anastomotic technique is used, some patients still develop a leak. The postoperative mortality rate in patients who did not leak was 1.7% but in patients who developed a leak after the same operation was 24.1%. Leaking anastomoses were associated with more postoperative respiratory problems (55.2 vs. 24.0%) and wound infections (65.5 vs. 14.8%) (Isbister, 2001).

During the period 1994-2001, the incidence of colorectal cancers was among the leading cancers (breast, lymphomas and leukemias) in Al-Jouf region of Saudi Arabia. The incidence of colorectal cancer was more in male population and the overall pattern was found to be similar to the findings in other regions of KSA (El-Hag *et al*., 2002). In a study on surgeries performed on 374 patients (Male and female ratio 1:0.9) in early (Dukes' Stages A-C) and advanced (Stage D) colorectal cancer, Isbister (2002) found no differences between the early and advanced colorectal cancer in perioperative requirements for either blood or total parenteral nutrition. There were no differences in perioperative morbidity or mortality in these groups.

## RESULTS AND DISCUSSION

A study on histopathological profile (tumor differentiation, tumor Duke's staging and grade of CRC) of 276 colorectal specimens in one of the hospitals of the Kingdom of Saudi Arabia during January 1996 to December 2000 revealed 1.5% of total endoscopic biopsies and 13.8% of colorectal biopsies. Among these cases, 81% were of mean age 56. Colorectal adenocarcinoma, cases were 7.6%, (mean age 35) signet cell carcinoma were 5%, (mean age 55.5), mucinous adenocarcinoma were 2.5% (age 68) metastatic papillary carcinoma, mixed mucin secreting signet cell carcinoma were 2.5% (age 64) and poorly differentiated squamous cell carcinoma was 2.5% (age 55). The study showed 21% of patients presented in their 3rd decade of life, 18.4% in the 4th decade, 15.8% in the 5th decade, 26.3% in the 6th decade, 10.5% in the 7th decade and 7.9% in the 8th decade (Mansoor *et al*., 2002).

In another study (January 1992 to December 1997) a total of 160 colorectal cancer, the male to female ratio was 1:0.8 and the mean age was 56.3+14.98 years. The age of onset was between 60 and 70 years. The duration of symptoms varied between 1-24 months with the majority of patients having symptoms for >6 months. The incidence of primary disease originating from rectum or sigmoid colon was 68.2 and 22.5% of patients had primary disease involving ascending and transverse colon. Patients with histologically determined adenocarcinoma were 82.5%. A total of 38.8% of patients were in Stage B and 38.1% of patients were in Stage C of Aster-Coller classification (Ayyub *et al*., 2002).

A 5 years study (1999-2004) on the pattern, sub site distribution and histological features of CRC in a hospital in Riyadh showed that the incidence was more in men and majority of the patients were younger than 40 years and had right sided colon cancers. The incidence of late Stage (III and IV) cancer was more than the early Stage (I and II) (Guraya and Eltinay, 2006). A tertiary hospital in Jeddah, received a total of 711 colonic biopsies during January 2000 to July 2007. Out of this, 477 biopsies showed inflammatory, nonspecific/infective and other miscellaneous colonic lesions, 181 (nonspecific colitis), 122 (ulcerative colitis), 15 (Crohn's disease) and 107 (benign polyps). The most dominant was adenomatous polyp, out of 99 malignant cases; 94 showed adenocarcinoma (Qayyum and Sawan, 2009).

In one of the referral hospitals of Riyadh, 50 patients (both sexes, aged around 50 years) were hospitalized for CRC. Most of the female patients were affected by gastrointestinal symptoms and 4% of the male patients had a family history of CRC. Although, the weight and height of the patients differed, there were no significant variations in body mass index. However, lack of knowledge of the benefits of high-fiber diet was a significant factor. The incidence of CRC was associated with low education level, unemployment and not taking regular exercise (Almurshed, 2009).

In a study on the incidence and role of p53 and DNA mismatch repair proteins in colorectal carcinomas, Al-Kuraya *et al*. (2006) evaluated the comparative frequency of major molecular pathways in colorectal cancers from Saudi Arabia. The researchers confirmed the associatioin between tumor phenotype and mismatch repair gene alteration in addition to the observation of a higher incidence of right sided location in Saudi than in

Western colon cancers. The high prevalence of mismatch gene expression loss defends for a higher importance of microsatellite instability.

The incidence of Microsatellite Instability (MSI), hereditary non polyposis colorectal cancer and tumor suppressor gene (*TP53*) mutations evaluated in Saudi colorectal carcinomas showed a high proportion of familial MSI cases and a lower incidence of TP53 mutations (Bavi *et al*., 2008).

Activation of the Phosphatidylinositol 3'-Kinase (PI3K)/AKT pathway results in an increase in cell proliferation and survival. Somatic mutations within the PI3K catalytic subunit, PIK3CA are common cause of increasing PI3K activity and are believed to be oncogenic in many cancer types. In a study on evaluation of PIK3CA mutational status in a series of 410 Middle Eastern CRC and 13 colon cell lines, Abubaker *et al.* (2008) reported a high prevalence of genetic alterations in PI3K/AKT pathway in Saudi cohort of CRC, predominance of PIK3CA mutations in the MSI subgroup and their possible involvement in development/progression of this subset of CRC.

An early event in CRC is the somatic mutation (KRAS) whose function and dysfunction in CRC is yet to be understood. In a study on KRAS mutation in CRC in Riyadh, Abubaker *et al.* (2009) investigated the relationship of KRAS variants (KRAS4A and KRAS4B) with various clinico-pathological characteristics in colorectal cancer. The analysis for KRAS mutation by direct DNA sequencing and immunehistochemical analysis after validation with real-time PCR assay. The *KRAS* gene mutations were seen in 80/285 CRCs (28.1%) KRAS4A protein expression was seen in the cytoplasm while KRAS4B protein was nuclear. The over expression of KRAS4A was significantly associated with left colon. The KRAS4A over expression was associated with a better overall survival. On the other hand, KRAS4B over expression was significantly associated with larger tumor size. The results focus the differential role of KRAS isoforms in CRC, their utility as a prognostic biomarker and underline the significance of KRAS alterations as a potential therapeutic target for CRC.

High Fatty Acid Synthase (FASN) is a metabolic enzyme associated with the synthesis of membrane phospholipids in cancer cells. Over expression of FASN is linked with activation of Phosphatidylinositol-3'-Kinase (PI3K)/AKT pathway. In a recent study, the functional association of FASN (a potential biomarker and a novel therapeutic target in distinct molecular subtypes of CRC) expression is determined with P13/AKT pathway in Middle Eastern CRC (Uddin *et al*., 2009). Folic acid supplementation was administered in specific dose and for specific duration to 805 patients of CRC in a local hospital, Riyadh, the treatment failed to prevent recurrence of adenomatous colorectal polyps (Ibrahim and Zekri, 2010). Taken together, most of the scientific research on CRC related on characterization, etiology and epidemiology of CRC and less attention focused on advances in genomic research of CRC.

## CONCLUSION

CRC is one of the most prevalent cancers throughout the world. With a poor prognosis in advance cases, more than one third of the patients die. The current treatment strategies are to cure only a fraction of the patients in the early stage. CRC is one of the few cancers in which molecular alterations are described to occur during disease progression. Most researches on molecular front of CRC began during the last decade in pre-millennium era and are more rampant in the third millennium. Although, there are progressive trends in researches involving CRC in KSA but a comparison with international progress reveals a lot to be done in this area. To meet the developmental targets, it is recommended that an aggressive approach of research is needed to understand the molecular alterations in CRC and to define new biomarkers and treatment strategies involving gene expression profiling using microarray technologies and MicroRNA techniques.

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