*Biomedical & Pharmacology Journal*, December 2018. Vol. **11**(4), p. 1773-1780

# The Prevalence and Evolving Risk Factors for Colorectal Cancer in the Arab World

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http://dx.doi.org/10.13005/bpj/1548

(Received: 30 October 2018; accepted: 06 December 2018)

**There is a global rise in the prevalence of colorectal cancer (CRC). Literature has shown an exponential growth in early detection and innovative strategies in treating CRC with some success. Despite preventive and screening measures, healthcare authorities have reported an increase in CRC in the Western as well as in the Arab world. Due to recent trend in adopting Western lifestyle by the Arab population, the current prevalence of CRC in the Arab world ranges from 19.8% to 38% and has been shown to affect younger population as well. In addition, new risk factors have been reported such as low serum levels of selenium and vitamin D, high use of food preservatives and microsatellite instability. Such emerging challenges in preventing and screening early CRC in the Arab world pose tremendous burden on healthcare authorities. In parallel with the state-of-art screening tools such as virtual colonoscopy and DNA-based stool immunohistochemistry tests, some *in vivo* endoscopic cytological examination by narrow band and confocal imaging have been introduced. The detection of microRNA-21 is being increasingly being used as a reliable biomarker for GIT cancers including CRC. Surgical resection of CRC remains the gold standard for CRC even in the presence of metastases. This research work underpins the prevalence of CRC globally as well as in the Arab world with special attention to emerging risk factors, early detection tools by nation-wide screening campaigns.**

**Keyword;** Colorctal cancer; Arab world; colorectal cancer screening; narrow band imaging; confocal examination; fecal immunohistochemistry.

There is a staggering rise of the incidence rate CRC worldwide till the last decade. However, although, recently the incidence rate of CRC has decreased, literature has signalled an exponential growth of CRC in population younger than 50 years. This changing pattern of incidence rate and epidemiology of disease presentation has also been observed in the Arab world. This research elaborates the magnitude of CRC globally and in the Arb world. In addition, an account of the emerging risk factors of CRC in the Arabian context is provided. Finally, the screening protocols for CRC and the innovative technological developments for *in vivo* cytological and imaging diagnosis of CRC are described. The need for underpinning the significance of protective factors and the use of state-of-the-art diagnostic and screening tools for CRC are emphasized.

**The global burden and pattern of colorectal cancer**

In the United States, colorectal cancer (CRC) is estimated to be the third most frequent cancer in both genders and second leading cause of cancer-related deaths (1) (2) (3). CRC accounts for

9.7% of all cancers worldwide, with approximately 814,000 cases in men and 664,000 in women (4). The incidence and mortality rates of CRC varies significantly by race and ethnicity. Colorectal cancer statistics in 2014 have shown that the incidence and death rates are highest in blacks and lowest in Asians/Pacific Islanders (5). Interestingly, death rates of 29.4 per 100,000 population in blacks were substantially higher than those in Asians/ Pacific Islanders (13.1) and in non Hispanic whites (19.2). Owing to more structured screening and surveillance programs, the incidence of CRC is decreasing by approximately 3% per year during 2001–2010). The biological characteristics of CRC is reflected by a peculiar pattern of subsite location in terms of age and gender. Women have a higher incidence of proximal cancers (46% vs 38%) and a lower risk of rectal cancers (24% vs 31%) (6). In addition, there is a profound increase in proximal and decrease in rectal cancers with advancing age.

**Magnitude of colorectal cancer in the Arab world**

Although, worldwide, the age-adjusted incidence of CRC is 20.1 per 100,000 men and 14.6 per 100,000 women, the reported incidences of CRC in the Arab world and Gulf Cooperation Countries (GCC) countries are relatively low (7). The Egyptian Gharbiah cancer registry has reported the incidence of $6.5/10^5$ for men and $4.2/10^5$ for women for the period of 2000–2002 (8). A population based study by Verttipong showed that the incidence rate of CRC for patients younger than 40 years in Egypt was slightly greater than the incidence of CRC in United States for the same age group (9). The dossier by the Cancer Incidence Report in Saudi Arabia has shown that the women develop CRC much earlier than men (45–59 vs. 60-74 years) (10) (11) . Five geographic regions of Saudi Arabia have been identified with the highest age-standardized incidence rates; Eastern (100.8/100,000), Riyadh (94.8/100,000), Makkah (77/100,000), Northern (71.3/100,000), and Tabuk (66.7/100,000) regions. However, no specific reason could be pinned down for the dissimilarities in incidence rates in different regions of Saudi Arabia. Deficiency of vitamin D has been claimed to be a major risk factor for several cancers including CRC and breast malignancies (12). A report by Hussein *et al*. has reported that 83.6% population in Saudi Arabia suffer from the vitamin D deficiency (13), while another study has shown that 100% of students from a Saudi University had severe vit D deficiency (14).

In the Eastern Mediterranean region (EMR), cancer is the fourth leading cause of death, after cardiovascular and infectious diseases and trauma (15) (16). In 2012, as many as 550,000 new cases and 360,000 deaths from cancer were reported for the EMR countries (4). The most commonly reported cancers were lung and CRC with a trend of higher incidence rates for CRC in population younger than 50 years. Interestingly, a report by Tore *et al*. has shown that the incidence of CRC is rising in certain countries where risk has been historically low particularly in Kuwait and Israel (17). A wide spectrum of environmental, dietary, and genetic factors contribute have been postulated to contribute to this epidemiological shift of CRC.

**Recent trend in colorectal cancer epidemiology**

Although recently we have witnessed a decline in the incidence of CRC people older than 50 years in the United States; however, new cases are expected to increase among younger population aged 20-49 years by 2030 (18). This finding is in agreement with the reports published from the Arab world that has signalled a rising incidence of CRC in young population under 50 years of age (7, 19). Evidence based clinical trials have shown that this staggering increase in the incidence of CRC among the young adult population is most likely driven by a dramatic shift in lifestyle and rising rates of morbid obesity among the Western populations (20) (21). There is a pressing need to conduct experimental and population based studies among younger populations to determine associations of CRC with excessive folate intake from over fortification, inflammatory bowel syndrome, rising incidence of infectious agents particularly human papilloma virus, preferences for more sedentary life style and high levels of sodium in food preservatives (22).

**Emerging risk factors for colorectal cancer in the Arab world**

The heterogeneity of CRC poses challenges to the scientists in elucidating a clear carcinogenetic pathway for this unique cancer. A wealth of risk factors have been shown to contribute to CRC such as family history, colonic adenomatous polyps, inflammatory bowel disease,

low selenium and vitamin D, and urban lifestyle (23) (24) (25). A wide spectrum of molecular markers have been hypothesised to the development and metastasis of CRC (26). The adhesive capacity of cell adhesion molecules, cadherins and catenins, enhances the metastatic potential of CRC (27). When downregulated, such substances facilitate disintegration of tumor cells that will determine the prognosis of CRC in human model (28). Intensive research in the molecular medicine has signalled a mix of exogenous (environmental) factors such as lifestyle and endogenous genetic factors (microsatellite instability) that play leading roles in molecular pathogenesis in cancer initiation, progression and response to therapeutic interventions (29). In a univariate analysis by Menendez *et al*., the researchers investigated the role of serum microRNA-21 in the carcinogenesis of CRC (30). The report inferred that relative overexpression of microRNA-21 was correlated with 51% low risk of CRC recurrence after curative therapy and microRNA-21 can be used as a reliable prognostic tool for CRC. In sharp contrast to these finding, a meta-analysis by Wang *et al*. investigated the diagnostic and prognostic value of microRNA-21 and the findings of this research have argued that higher expression of serum microRNA-21 was associated with worse survival (31). Thus the expression of microRNA-21 as a predictor of prognosis and reliable tool for diagnosis of CRC is still debatable and needs further research.

Some dietary population based studies from the Middle East have reported high consumption of red meat, animal fats, and a low consumption of fresh vegetables and fruits contribute to a typical dietary profile for CRC (32). An adequate supply of dietary antioxidants plays a crucial role in the primary prevention of oxidative stress-mediated ailments such as CRC (33). In this perspective, a study has reported low intake of dietary antioxidants among CRC subjects in contrast to the controls in a Saudi population (34). As emphasized before, a normal serum vitamin D level inhibits oncogenes in the colonic epithelium and vitamin D deficiency leads to an uninhibited cascade of epithelial proliferation. Thus, several modifiable dietary factors play key roles in the carcinogenesis of CRC.

**Prevention of colorectal cancer**

Research has shown certain protective factors that potentially provide defence against the development of CRC. A meta-analysis by Chan and Giovannucci has inferred that the risk of CRC was reduced by 20% to 30% by regular physical activity as compared with those who were less active (35). Literature has also eluded the potentially protective role of Aspirin (acetylsalicylic acid) and non-steroidal anti-inflammatory drugs (NSAIDs) against CRC (36). Supplementation of vitamins A, C, D, and E and folate and fiber in diet has been shown to prevent and arrest the development of CRC (37). However, there is no concrete evidence that the regular use of these supplements can decrease the incidence rate of CRC (38). Similarly, several evidence-based clinical trials have elucidated the protective role of calcium supplementation in CRC (39).

Unfortunately, literature search has shown scantly evidence at the national level from the Arab world that can convincingly enforce the protective measures as public campaigns.

**Screening colorectal cancer**

CRC is peculiar in presenting late and with a wide spectrum of clinical manifestations particularly when advanced (23) (40). The acumen of physicians need to be enhanced to identify CRC at an early stage that can facilitate effective treatment with improved prognosis (41) (42). The surgical trainees and even established surgeons have to upskill their surgical skills to keep abreast with rapidly emerging technological innovations (43) (44). Currently, a range of screening protocols have been employed by different healthcare facilities. CRC screening strategies include sttol based tests, imaging, and endoscopic method.

**Stool based tests**

Heme and globin moieties are produced from haemoglobin breakdown in the gut. The *guaiac fecal occult blood testing* (gFOBT) identifies heme through peroxidase reaction. Red meat and certain vegetables interfere with the analysis and patients are instructed to avoid them few days before this test. Doses of vitamin C higher than found in multivitamin, can potentially lead to false-positive result and should be avoided before testing. Subjects are instructed to apply stool to a guaiac card from 3 consecutive bowel movements

and then cards are examined in physicians' office with a reagent (45). The estimated sensitivity of gFOBT test ranges from 64% to 80% for detection of CRC and a positive test mandates colonoscopy (46).

Another stool based test if *fecal immunochemical test* (FITs) that use antibodies specific to the globin moiety of hemoglobin. Such testing dos not employ peroxidase activity and thus the results are not influenced by dietary changes. Only one single stool card is used. Understandably, the absence of dietary restrictions and single use of stool card increase patients' compliance with FIT (47). Since FIT tests detects blood from colonic origin, the chances of false positive by bolodd from upper GIT are minimal. Nevertheless, the sensitivity of FIT for detecting CRC is similar to gFOBT (48). The recent master-class development in stool-based test is the introduction of *FIT testing for hemoglobin with DNA* (Cologuard; Exact Sciences). This test identifies cells that are shed into the stool by CRC (49). The described stool based tests can be conveniently performed at home without disturbing routine work. However, these tests are unable to identify majority of polyps as most of the polyps do not bleed (50).

**Endoscopy**

*Flexible sigmoidoscopy* enables visualisation of rectum, sigmoid and descending colon upto 60 cm from the anal verge. The estimated sensitivity of flexible sigmoidoscopy ranges from 60% to 70% for detecting CRC and advanced adenomas (50). Although flexible sigmoidoscopy can be easily performed in offices, since the proximal colon is not visualised, approximately one-third of adenomas and CRC in the right colon can be missed (50). *Colonoscopy* is a popular screening tool worldwide and carries the highest sensitivity of 85% to 96% for detecting CRC and as well as precancerous polyps (50). Flexible sigmoidoscopy is performed in office without sedation, however, colonoscopy needs full bowel preparation and conscious sedation.

**Imaging**

Computed tomography colonography (CTC) is an advanced diagnostic imaging procedure which uses x-rays and computers to produce two- and three-dimensional images of the colon. There is little or no need for bowel preparation and the procedure is performed by distending the colon with $CO_2$ (51). When performed during CRC screening, CTC can detect polyps for precancerous growths. There is an estimated sensitivity of 93% and specificity 97% for polyps larger than 1 cm in size, 86% sensitivity for polyps 6 mm to 1 cm, and 45–97% sensitivity for polyps smaller than 6 mm (52). There is general consensus among radiologists that lesions larger than 10 mm should be referred for colonoscopy. However, for colonic lesions between 6 and 9 mm there is no agreement but majority of radiologists would suggest a follow-up CTC in 3 years, though, the American Collee of Radiologists recommends colonoscopy (53).

The estimated dose of radiation with a CTC is 7 to 13 mSv that carries a hypothetical risk of cancer due to exposure to radiation (54). There is also a 0.005% risk of bowel perforation by CTC. Nevertheless, rate of complications from CTC remains low and this diagnostic tool is being increasingly used in CRC screening programs.

**Screening protocols**

A recent review by Smith *et al*. has divided the current American Cancer Society guidelines for CRC into two groups; 1) tests that *primarily* detect cancer such as gFOBTs and FITs and stool tests for exfoliated DNA; and 2) tests that can detect cancer and advanced lesions including endoscopic and radiological examinations, flexible sigmoidoscopy, colonoscopy, double contrast CT and colonography (or virtual colonoscopy) (55). The dynamics of screening programs are mostly chosen by the individual risk, personal preference, and the available of resources and expertise. "Thus for an average risk adult CRC screening is recommended at the age of 50 years with *one* of the following options: 1) annual high sensitivity gFOBT or FIT; 2) an sDNA test every 3 years; 3) flexible sigmoidoscopy every 5 years; 4) colonoscopy every 10 years; 5) double contrast barium enema every 5 years; or 6) CT colonography every 5 years" (55).

Unfortunately, a unified standard CRC screening guideline is lacking in the Arab world. At the same time, over judicious use of certain screening tools not covered by recommended guidelines may potentially adversely influence the effectiveness of screening and early detection of real cases of CRC (56). Most high income countries implement population based colorectal cancer screening programs, but most of the

Arab world countries don't apply nation-wide screening programs due to several cultural and religious barriers and absence of public awareness campaigns. There is a pressing need for a concerted effort in drafting and implementing CRC screening guidelines that can cater the Arab world.

**Using modern technological innovations to diagnose colorectal cancer; in vivo cytological examination**

In addition to the available diagnostic tools for CRC, a wealth of cutting-edge technologies have introduced several endoscopic and imaging methods that can facilitate in-vivo cytological diagnosis of CRC (57). *Narrow band imaging* is a modern optical tool that carries the potential to clearly visualize microvasculature of organ surface and distinguishes between neoplasia and non-neoplastic growths by precisely demonstrating the pit pattern and structure (58). This diagnostic modality is increasingly being used to identify an unknown lesion, to define a sharp margin between normal and pathological lesion, and to accurately determine benign, dysplastic and malignant nature of lesion. *Confocal laser endomicroscopy* examines living cells during endoscopy and enables virtual histological examination of neoplastic growths with immaculate accuracy and precision (59). Architecture distortion with heterogeneous backscattering of signal and a bizarre mucosal surface indicate malignant transformation. *Optical coherence tomography* identifies angiographic proliferation with comprehensive imaging of the mucosal and submucosal structures of the GIT (60). Of all the aforementioned diagnostic tools, *endoscopic ultrasound* is the most popular and widely used diagnostic device globally as well as in the Arab world. This examination provides information about submucosal, extramural, epithelial lesions as well as aids in endoscopic fine needle aspiration cytology of suspected colorectal lesions (61). Endoscopic ultrasound has an estimated sensitivity of 97%, specificity 100%, positive predictive value 100%, and an accuracy of 98% (62). Since the diagnostic accuracy of the tools for in vivo cytological evaluation for CRC are still being tested, so far, endoscopic ultrasound has proved to be most valuable clinical adjunct in the management of CRC.

## CONCLUSIONS

Though there is a rising incidence rate of CRC in men under 50 years of age in the Arab world, there is no concomitant concerted effort for screening CRC in the region. There is a need to intensify screening protocol and to raise public awareness to empathize the significance of CRC screening for early detection and better prognosis. In addition to colonic polyps, inflammatory bowel disease, and family history, consumption of animal fat, preservatives with excess sodium, low serum vitamin D levels, and less physical activity can potentially lead to CRC. Most of these risk factors are witnessed in the Arab world with their highest impact. Reducing the age of screening programs from 50 years may potentially reduce the incidence of CRC among younger age groups, though, at the cost of economic and financial burden. Modern technologies have enabled to diagnose CRC *in vivo* by using virtual cytological examination such as narrow band imaging and optical coherence tomography. However, there is little evidence that such modern diagnostic tools are in practice in the Arab world, except for the use of endoscopic ultrasound. Sufficient training and applications for in vivo cytological examination can potentially identify early CRC with excellent prognosis, if treated appropriately.

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