Micha Barchana

BACKGROUND

Environmental and Lifestyle Risk Factors

Colorectal cancer (CRC) is common in the Western world and usually ranks high in incidence and mortality among malignancies in those countries. Two observations have led researchers to look for diet and lifestyle as explanatory factors of risk for CRC. First, ecological studies comparing large populations have shown that rates of CRC differ dramatically among countries, varying by as much as 10-fold, from low-incidence areas in Asia and Africa, to much higher rates in northern Europe and the United States. Second, studies have shown that migrants from low-risk areas to high-risk Western countries experience rapid increases in CRC risk within the same generation *[1-5]*. Diet appeared to be the major explanatory factor for these phenomena: Namely, low consumption of red meat and dietary fat and high consumption of fiber in Asian and African countries, with an opposite dietary pattern in northern Europe and the United States. Recent data, however, do not support an association between dietary fiber and risk of CRC *[6-8]*. Emerging data suggest that low levels of physical activity and greater adiposity increase risks *[9-11]*. Since high levels of physical activity and low rates of adiposity characterize low-risk countries in general, these factors may account for much of the international differences in CRC rates. In other studies, cigarette smoking has been associated with increased risks of CRC, as has high alcohol consumption. These findings were reported in many, although not all, studies, and the role of tobacco and alcohol use in the etiology of CRC has yet to be determined *[12-18]*. On the other hand, there are several known protecting factors. Nonsteroidal anti-inflammatory drugs, in particular aspirin, are thought to be protective *[19,20]*. Calcium supplementation has been shown in randomized studies to reduce the recurrence of adenomatous colorectal polyps that are thought to be precursors to CRC *[21,22]*. On the behavioral side, it has been shown that physical activity and maintaining a desired body mass index may reduce the occurrence of CRC *[10,23]*.

Genetic Risk Factors

The essential element in the etiology of CRC is a process of genetic change in the epithelial cells of the colonic mucosa *[24,25]*. Chief among the factors that can initiate CRC development is a predisposition to mutagenic effects, where metabolic pathways may be altered by polymorphisms in genes responsible for detoxifying mutagens. Thus, differences in polymorphisms among individuals can account for their differing susceptibility to mutagens from the diet. Fecal mutagens in the stool may be produced by the interaction of digestion and food products. Changes in the fecal microflora indicate that changes in diet may alter mutagenic activity by altering extracellular superoxide formation *[26]*.

Family history – the occurrence of CRC in a first- or second-degree relative – is an identified risk factor for CRC. An increased risk among siblings of an affected person has been observed, and in one study was particularly high for cancer in the proximal colon (from the cecum up to the distal third of the transverse colon) *[27]*. An increased risk has also been observed among children of affected persons, both for CRC overall and for cancers of the proximal colon, distal colon, and rectum, with relative risks of approximately 1.8 *[28]*.

People affected with inflammatory bowel disease, either Crohn's disease or ulcerative colitis, are at increased risk for developing cancers of the gastrointestinal tract, particularly CRC *[29]*. The current literature suggests that these persons have a genetic predisposition to CRC and that long-standing inflammation is not of primary importance in the promotion of cancer *[30-34]*.

Familial polyposis syndromes are characterized by the early onset of multiple polyps and a very high risk of CRC development *[35]*. These syndromes have autosomal dominant inheritance with high but variable penetrance. Hereditary nonpolyposis colon cancer (HNPCC) syndrome is inherited as an autosomal dominant trait with high penetrance. Its phenotypic features are early-onset CRC (mean age: 46 years), multiple synchronous or metachronous CRCs (35%), and CRCs usually, but not always, located in the proximal colon *[36]*. HNPCC cancers are more likely to be signet-ring cancers and poorly differentiated, with extensive inflammatory infiltrates *[37,38]*. Particularly relevant to this MECC report is the feature of inherited CRC in Ashkenazi Jews (Jews of European origin). Israeli Ashkenazi Jews have the highest CRC incidence of any Israeli ethnic group. There are reports of a missense mutation (I1307K) in the *APC* gene, unique to Ashkenazi Jews and found in 6% of the Ashkenazi Jewish population and in 28% of those in this population with a family history of CRC. Among the carriers of the mutation, CRC is found in 13% of those who have polyps *[39,40]*. There do not appear to be any differences in clinical presentation between carriers of the mutation and noncarriers, so genetic testing in this population may be required to identify high-risk individuals for screening.

Early Detection

CRCs are among the very few cancer sites where screening and early detection are both feasible and proven to reduce mortality. The recommended test for mass screening is the fecal occult blood test (FOBT), which has been extensively studied and used since the early 1980s. This test, which acts as a first screen for possible malignancy, is designed to detect blood traces in the stool on a guaiac-based testing sample. Persons testing positive usually undergo colonoscopy as a more invasive but definitive examination. Newer technologies combine the guaiac-based test with tests based on molecular biology to look for cancer biomarkers in the stool. Serial guaiac-based FOBT is simple, inexpensive, and proven effective at reducing mortality from CRC. Immunochemical FOBT facilitates compliance and offers improved specificity, but at increased cost relative to guaiac-based FOBT. Fecal DNA testing may provide enhanced sensitivity for detection of CRC compared with FOBT, but its high cost limits its use for generalized screening. Other noninvasive tests, such as rectal mucin testing, have been developed more recently and require evaluation and comparison with guaiac-based FOBT. Serum tests, such as proteomics, nuclear matrix proteins, and serum DNA, are still in their infancy but remain a hope for the future *[41-46]*.

More direct methods for detecting colonic premalignant and malignant tumors include the use of colonoscopy or flexible sigmoidoscopy *[47,48]*. An exciting new CRC screening option is virtual colonoscopy (VC), which, by screening out persons without neoplasia, allows colonoscopy to be reserved for those requiring therapeutic intervention. The sensitivity of VC for large adenomas and CRC appears to be high, although results vary by center, and sensitivity for small adenomas is low. Some investigators have suggested that VC might be a useful option for investigating patients who test positive with stool-based screening tests *[49-51]*. Because no CRC screening technology program has been implemented in a substantial proportion of any MECC population, screening has yet to reduce the incidence or mortality of CRC in the Middle East.

Worldwide Incidence

Globally, the age-standardized incidence rate (ASR) of CRC is 20.1 per 100,000 males and 14.6 per 100,000 females. As mentioned earlier, there are notable differences between CRC incidence rates in more developed versus less developed countries. In the developed parts of the world, the ASR is 40.0 in males and 26.6 in females; in less developed areas, the rates are 10.2 and 7.7, respectively. The highest ASRs in males are observed in Australia/New Zealand (48.2), followed by North America (44.4) and Western Europe (42.9). At the other end of the scale, the rates in South-Central Asia (4.7) and Central Africa (2.3) are lowest *[52]*.

Incidence-to-mortality ratios also differ substantially between developed and less developed countries. The rate ratio varies from 2.9 in North America (indicating 2.9 incident cases for every death

from CRC) to 1.0 in Central and North Africa (indicating that for every new case of CRC, there is a death from this cancer) *[52]*.

The pattern of CRC incidence rates in females is similar to that in males, with the Australian continent presenting the highest rate (36.9), followed by North America (32.9). The lowest CRC rates in females are found throughout Africa (3.3-4.0), except South Africa, and also in South-Central Asia (3.5). Incidence-to-mortality rate ratios are high in North America and Australia (2.8 and 2.6, respectively) and low in all African countries (1.07-1.10), except South Africa *[52]*.

RESULTS

The total number of CRC cases reported to the registries during the study period was 74,369: 455 cases in Egyptians, 550 in Israeli Arabs, 697 in Cypriots, 1,654 in Jordanians, 15,533 in Israeli Jews, and 55,480 in US SEER (see Table 1.5).

Data Quality Indices

The gold standard for defining a cancer is the microscopic proof of malignant cells. Cancer registries rely, for the most part, on histological or cytological reports when defining incident cases. However, cancer registries collect information from other sources, such as death notifications and imaging procedures, that can supply information of lesser accuracy on the disease. The percentage of microscopically confirmed cases is often used as a quality indicator. Another way to assess quality of data is through the coding of subsites. The coding system adopted by MECC countries, the International Classification of Diseases in Oncology (ICD-O) (3rd edition), is based, for CRCs, on the anatomic location of the lesion, and reserves a code for a more general definition: "Colon, not otherwise specified (NOS)." This term is usually reserved for those cases where the exact location of the tumor cannot be accurately defined. The percentage of use of this more general code can also be used as a measure of accuracy.

Table 4.1 shows the percentage of microscopically confirmed total cases and the percentage of cases coded "Colon, NOS" for each of the populations.

The percentage of microscopic confirmation of CRC varied between 84.6% (Egypt) and 99.0% (Cyprus and Jordan). The higher values correspond to registries that do active registration where patient data and records are easily accessed for further exploration, but a very high value may also indicate that death certificates are not used, which would result in underestimated incidence rates. The US SEER microscopic confirmation rate was high (97.5%), but SEER has an

Table 4.1. Colorectal Cancer: Proportions of Total Cases Microscopically Confirmed and of Cases Coded "Colon, NOS"* in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001

Registry	Proportion Microscopically Confirmed	Proportion Colon, NOS*
Cyprus 1998-2001	99.0%	20.1%
Israel (Jews) 1996-2001	91.4%	17.7%
Israel (Arabs) 1996-2001	91.5%	17.8%
Egypt 1999-2001	84.6%	23.1%
Jordan 1996-2001	99.0%	35.9%
US SEER† 1999-2001	97.5%	2.9%

*NOS indicates "not otherwise specified."

†SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

active follow-up program to check cases that are initially found by death certificate.

The percentage of cases coded "Colon, NOS" was 20.1% for Cypriots, 17.7% for Israeli Jews, 17.8% for Israeli Arabs, 23.1% for Egyptians, 35.9% for Jordanians, and 2.9% for US SEER (Table 4.1). A large proportion of cases coded in this less accurate way can result in less accurate data, although it should not greatly impact the estimates of overall incidence of CRC.

Overall Rates

As mentioned earlier, CRC is one of the most common cancers in the Western world, and constitutes about 13% of all cancers occurring in these countries. In MECC countries, CRC in Israeli Jews constituted 14.8% of all new cases in this population, followed by Cypriots and US SEER, where it was approximately 11% of all new cancer cases. Among Israeli Arabs and Jordanians, only approximately 9% of cancers were CRC, and in Egypt, 4.4%. (See Table 1.6.)

Observing the incidence rate of CRC (Table 4.2), we can subdivide the MECC countries into high-, middle-, and low-incidence countries. Israeli Jews had the highest incidence rate among all the populations considered (36.9). The ASR for Israeli Jewish males was 41.7, followed by US males (37.7), Israeli Jewish females (33.3), and US females (27.4). Cypriots had a lower incidence rate (17.3), similar to that of Israeli Arabs (15.2). Jordanians and Egyptians presented the lowest rates: 11.3 and 6.0, respectively.

The male-to-female incidence rate ratio (IRR) is another characteristic of CRC patterns. In developed countries, the male-to-female IRR tends to about 1.5, and in less developed countries it is about 1.3 *[52]*. In the MECC data, the IRR was 1.38 for US SEER, 1.35 for Egyptians, 1.27 for Israeli Arabs, 1.25 for Israeli Jews, 1.19 for Cypriots, and 1.03 for Jordanians. These findings do not completely follow the general trend of higher IRRs in more developed countries (Table 4.2)

Table 4.2. Colorectal Cancer: Number of Cases and Age-Standardized Incidence Rates,* by Age and Sex, in Cyprus, Israel, Egypt, Jordan, and US SEER − 1996-2001†

	Cyprus 1998-2001			Israel (Jews) 1996-2001			Israel (Arabs) 1996-2001			Egypt 1999-2001			Jordan 1996-2001			US SEER‡ 1999-2001		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total cases	697	355	342	15,533	7,805	7,728	550	287	263	455	261	194	1,654	845	809	55,480	27,892	27,588
Total rate*	17.3	19.0	16.0	36.9	41.7	33.3	15.2	17.3	13.6	6.0	6.9	5.1	11.3	11.5	11.2	32.0	37.7	27.4
<40 y	1.2	*1.2*	*1.1*	1.0	1.0	1.1	1.0	0.7	1.4	1.4	1.7	1.1	1.2	1.1	1.2	1.2	1.3	1.2
40-59 y	20.1	17.6	22.7	40.5	38.9	42.0	21.6	22.6	20.6	13.3	13.4	13.1	20.9	18.4	23.7	37.9	43.3	32.8
60-69 y	84.5	96.6	73.8	181.1	210.6	156.9	76.4	80.2	73.1	19.6	27.2	12.4	52.6	54.0	51.0	154.0	185.4	126.4
70+ y	159.2	193.4	132.3	374.0	451.5	318.4	116.5	161.2	80.0	20.8	25.1	17.1	60.7	78.6	44.4	311.3	369.8	270.8

*Rates are per 100,000 and are age-standardized to the World Standard Million.

†"*[Numeral]*" (italic) = 0 or 3-15 cases.

‡SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Colon versus Rectal Cancers

The MECC project focuses on cross-sectional data collection and does not include data on trends of the disease. Data on secular trends in CRC incidence emphasize the different behavior of cancers of the colon and rectum. Colon cancer incidence has been rising in the last decade in many developed and developing countries, and rectal cancer incidence has been falling. The pattern of CRC site incidence in industrialized and "Westernized" countries is that of a decrease in rectal cancer and an increase in proximal colon cancer. This has been noted worldwide in diverse populations *[53-68]*. The United States has the unique pattern of a decreasing incidence of total CRC and distal (left-sided) CRC, but a stable incidence of proximal right-sided CRC *[69]*. In many countries, the increase in proximal CRC has been noted to be more prominent in females *[70]*. Norway and Denmark are exceptional because distal is more prominent than proximal CRC in these countries *[67,71]*. Reasons for the changing CRC trends and the epidemiology of the CRC site distribution are assumed to be related to changes in diet and lifestyle associated with industrialization *[56]*. Worldwide, industrialization is associated with an increasing life expectancy, especially among females, and there is now a substantially increased proportion of females who are older than 65 years *[38,72]*. However, the reason for their greater tendency to develop proximal cancer is unclear.

Table 4.3 shows the colon-to-rectal cancer IRR in some selected countries *[73]* and for MECC populations for the years 1993-1997. According to the above theory, industrialized countries would tend to have more colon cancer and less rectal cancer, and therefore higher colon-to-rectal cancer IRRs. The table shows that the MECC populations did not follow this pattern, with Egyptians and Jordanians (less industrialized populations) having IRRs only a little lower than those of US SEER Whites, and higher than those in China and Poland. However, Israeli Jews (a more industrialized population) did have a high IRR.

Subsites of Colorectal Cancer

Proportions of cases diagnosed by anatomic location within the colon (excluding the rectum) are presented in Figure 4.1. It is difficult to interpret the data from Egypt and Jordan because a substantial proportion of the cases are coded "Colon, NOS." The proportion of ascending colon cancer appears similar in the United States and Israel and accounts for about 15% of all colon cancers, whereas in Cyprus, ascending colon cancer accounts for about 5% of cases. Cancers of the cecum occur in greater proportions in Cyprus and the United States (15% and 21%, respectively) than in Israel (less than 10%). The sigmoid colon is involved in about 30% of

Table 4.3: Colorectal Cancer: Age-Standardized Incidence Rates* and Incidence Rate Ratios (IRR) of Colon and Rectal Cancers in Selected Countries and in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1993-1997

Country/Registry	Male			Female		
	Colon	Rectum	IRR	Colon	Rectum	IRR
Canada	25.7	15.8	1.6	19.8	8.8	2.2
China - Shanghai	11.5	9.0	1.3	12.0	7.5	1.6
Japan - Osaka	24.7	15.1	1.6	15.5	7.3	2.1
Denmark	20.5	17.6	1.2	18.4	11.2	1.6
Poland - Krakow	14.5	11.7	1.2	10.4	6.9	1.5
Cyprus	12.7	6.3	2.0	11.2	4.8	2.3
Israel (Jews)	29.6	12.1	2.4	24.7	8.6	2.9
Israel (Arabs)	10.5	6.8	1.5	9.4	4.2	2.2
Egypt	4.6	2.3	2.0	3.3	1.8	1.8
Jordan	7.6	3.9	1.9	7.2	4.0	1.8
US SEER (Whites)	25.9	13.0	2.0	19.6	8.2	2.4
US SEER (Blacks)	32.3	12.7	2.5	26.0	8.2	3.2

*Rates are per 100,000 and are age-standardized to the World Standard Million.

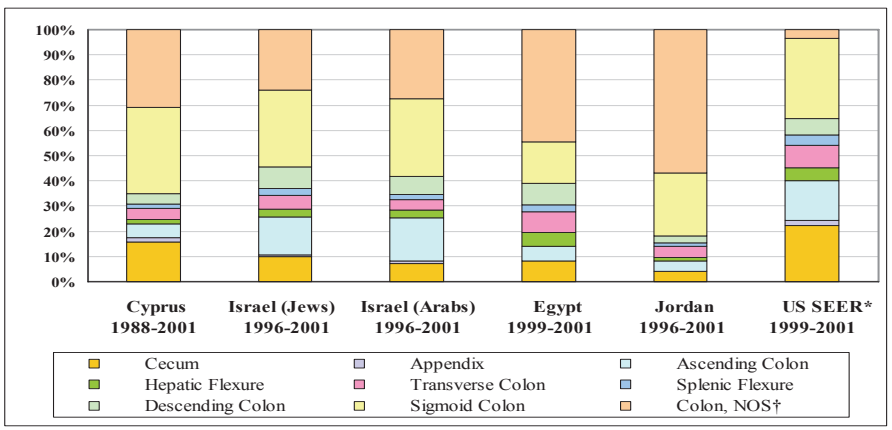
Source: Parkin, D. M., Whelan, S. L., Ferlay, J., Teppo, L., and eds. Cancer incidence in five continents, volume VIII. Lyon (France): International Agency for Research on Cancer; 2002. IARC Scientific Publication No. 155.

colon cancers in Cypriots, Israeli Jews and Arabs, and US SEER. Cancers involving the transverse colon occur in about the same proportion in the Israeli populations and in Cypriots (4% to 5%), but the proportion is higher in US SEER (about 9%). In Israel, the percentage of descending colon cancers is somewhat higher (8%) than in US SEER and Cyprus (6% and 4%, respectively).

Age-Specific Incidence Rates

CRC is rare under 40 years of age, and rates begin to rise sharply after this age. By the age of 40 to 59 years, Israeli Jews and the US SEER population had a substantially higher rate (about 40) than the other populations (13 to 22). The same pattern, with Israeli Jews and US SEER having the highest age-specific rates, occurred in all age groups over 40 years (Table 4.2). Figure 4.2 presents the pattern graphically, showing ASRs by 5-year age groups for ages 50 years and above. Rates in Israeli Jews and the US SEER population display a sharp rise with age, while rates in the other populations increase with age more slowly. In fact, rates remain almost invariable from the age of 50 years in Egyptians, who have very low rates. In Jordanians and Israeli Arabs, the rates rise by about 20% and 40%, respectively, for each 5-year period between the ages of 50 and 75 years. In Cypriots, the percentage rise per 5-year period over this age range is about 50%, which is the same as the rise in Israeli Jews and US SEER. However, because the Cypriot rate at age 50-54 years is about half that of Israeli Jews and the US SEER population, the 50% rise in the Cypriot rate constitutes a much smaller increase.

Figure 4.1. Colorectal Cancer: Proportions of Colon Cancers Diagnosed in Different Anatomical Subsites in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER – 1996-2001

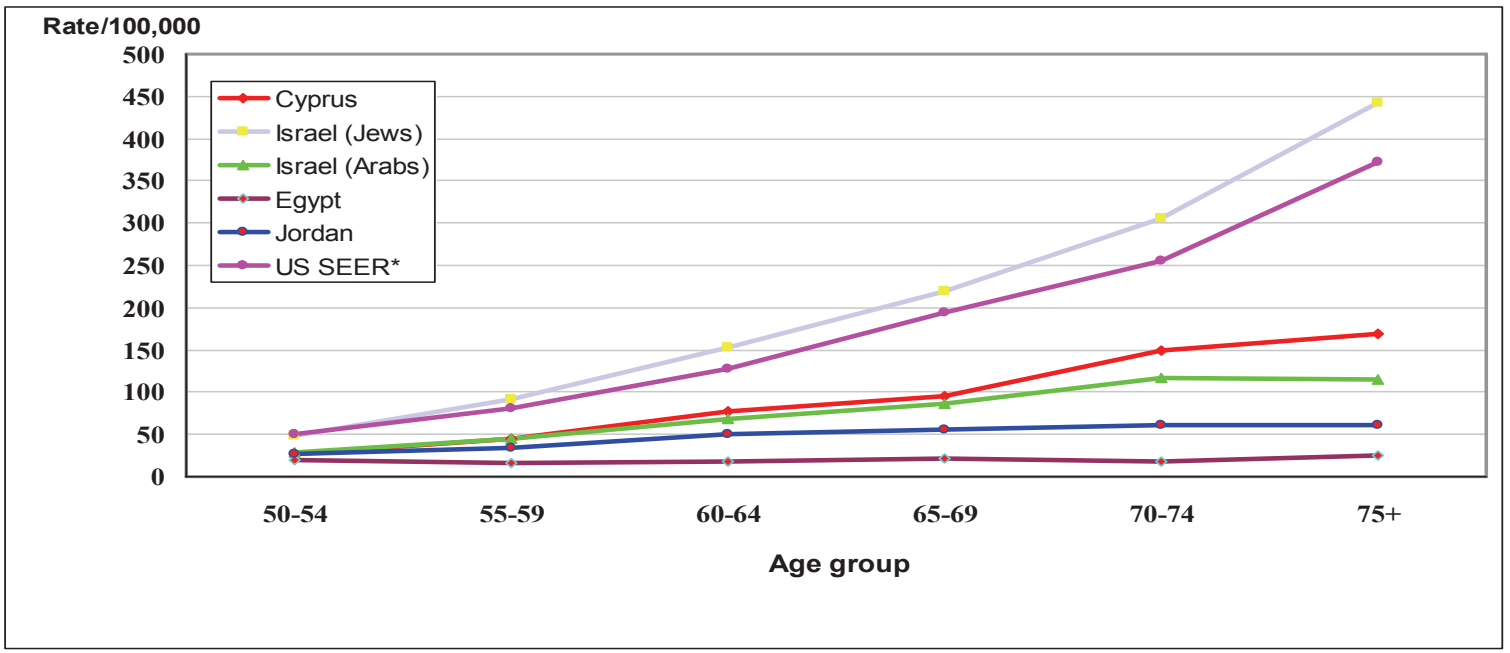


*SEER 13 Registries, Public Use Data, from data submitted November 2004.
†NOS indicates not otherwise specified.

SUMMARY AND CONCLUSIONS

The comparison of incidence rates among several Middle Eastern populations provides the opportunity to explore one of the most significant types of cancer in a new perspective. The comparison comprises 4 countries and 5 subpopulations situated in close proximity that have some similarities and also some marked differences in lifestyle. Egypt and Jordan are classified by the World Bank *[74]* as developing countries, while Cyprus and Israel are considered developed countries. The data presented support the existence of a link between economic status and CRCs, where higher rates were observed in Israeli Jews (similar to US rates) and, to a lesser extent, in Cypriots. The burden of CRC was high among Israeli Jews (higher even than in the United States), and other published data show very high rates among Israeli Jews originating from European countries *[70]*. The high socioeconomic status and the elevated rate of genetic mutations and polymorphisms in this subpopulation are probably both factors related to the increased incidence of CRC. The very low incidence of CRC in Egypt might be explained by other competing diseases (e.g., carcinoma of the urinary bladder), low detection rates, or local nutritional factors that are protective.

Figure 4.2. Colorectal Cancer: Age-Specific Incidence Rates in 5-Year Age Groups for Ages 50 Years and Older in Cyprus, Israel (Jews and Arabs), Egypt, Jordan, and US SEER − 1996-2001



*SEER 13 Registries, Public Use Data Set, from data submitted November 2004.

Colon cancer was more common than rectal cancer in all the MECC populations studied, and it constituted over 65% of all CRCs. Examination of the rates of proximal and distal cancers confirms the pattern of a greater proportion of proximal cancers in the more industrialized populations.

This comparison can add to the already established observation that CRC is mainly a result of lifestyle and behavior, including diet and body mass. The correlation found in this comparison between CRC incidence and level of economic development of the various populations is consistent with published literature that more developed countries present with higher rates. It would be interesting to conduct further research in this direction, especially to study in greater depth the apparently low incidence rates presented for Egypt.

REFERENCES

[1] Nilsson B, Gustavson-Kadaka E, Rotstein S, Hakulinen T, Rahu M, Aareleid T. Cancer incidence in Estonian migrants to Sweden. Int J Cancer 1993;55:190-5.

[2] Monroe KR, Hankin JH, Pike MC, Henderson BE, Stram DO, Park S, et al. Correlation of dietary intake and colorectal cancer incidence among Mexican-American migrants: the multiethnic cohort study. Nutr Cancer 2003;45:133-47.

[3] Wogan GN. Diet and nutrition as risk factors for cancer. Princess Takamatsu Symp 1985;16:3-10.

[4] Levin KE, Dozois RR. Epidemiology of large bowel cancer. World J Surg 1991;15:562-7.

[5] Kune S, Kune GA, Watson L. The Melbourne colorectal cancer study: incidence findings by age, sex, site, migrants and religion. Int J Epidemiol 1986;15:483-93.

[6] Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan. Br J Cancer 2005;92:1782-4.

[7] Michels KB, Fuchs CS, Giovannucci E, Colditz GA, Hunter DJ, Stampfer MJ, et al. Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. Cancer Epidemiol Biomarkers Prev 2005;14:842-9.

[8] Campos FG, Logullo Waitzberg AG, Kiss DR, Waitzberg DL, Habr-Gama A, Gama-Rodrigues J. Diet and colorectal cancer: current evidence for etiology and prevention. Nutr Hosp 2005;20:18-25.

[9] Steindorf K, Jedrychowski W, Schmidt M, Popiela T, Penar A, Galas A, et al. Case-control study of lifetime occupational and recreational physical activity and risks of colon and rectal cancer. Eur J Cancer Prev 2005;14:363-71.

[10] Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005;7:204-13.

[11] Cerin E, Leslie E, Bauman A, Owen N. Levels of physical activity for colon cancer prevention compared with generic public health recommendations: population prevalence and sociodemographic correlates. Cancer Epidemiol Biomarkers Prev 2005;14:1000-2.

[12] Correa Lima MP, Gomes-da-Silva MH. Colorectal cancer: lifestyle and dietary factors. Nutr Hosp 2005;20:235-41.

[13] Zimmerman DD, Gosselink MP, Mitalas LE, Delemarre JB, Hop WJ, Briel JW, et al. Smoking impairs rectal mucosal bloodflow – a pilot study: possible implications for transanal advancement flap repair. Dis Colon Rectum 2005;48:1228-32.

[14] Luchtenborg M, Weijenberg MP, Kampman E, van Muijen GN, Roemen GM, Zeegers MP, et al. Cigarette smoking and colorectal cancer: APC mutations, hMLH1 expression, and GSTM1 and GSTT1 polymorphisms. Am J Epidemiol 2005;161:806-15.

[15] Perez-Holanda S, Rodrigo L, Vinas-Salas J, Pinol-Felis C. Effect of ethanol consumption on colon cancer in an experimental model. Rev Esp Enferm Dig 2005;97:87-96.

[16] Chen K, Jiang Q, Ma X, Li Q, Yao K, Yu W, et al. Alcohol drinking and colorectal cancer: a population-based prospective cohort study in China. Eur J Epidemiol 2005;20:149-54.

[17] Yeh CC, Hsieh LL, Tang R, Chang-Chieh CR, Sung FC. Vegetable/fruit, smoking, glutathione S-transferase polymorphisms and risk for colorectal cancer in Taiwan. World J Gastroenterol 2005;11:1473-80.

[18] Larsson SC, Giovannucci E, Wolk A. A prospective study of dietary folate intake and risk of colorectal cancer: modification by caffeine intake and

cigarette smoking. Cancer Epidemiol Biomarkers Prev 2005;14:740-3.
[19] Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 2005;294:914-23.
[20] Courtney ED, Melville DM, Leicester RJ. Review article: chemoprevention of colorectal cancer. Aliment Pharmacol Ther 2004;19:1-24.
[21] Weingarten MA, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Cochrane Database Syst Rev 2005;CD003548.
[22] Pence BC. Role of calcium in colon cancer prevention: experimental and clinical studies. Mutat Res 1993;290:87-95.
[23] Chao A, Connell CJ, Jacobs EJ, McCullough ML, Patel AV, Calle EE, et al. Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2004;13:2187-95.
[24] Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525-32.
[25] Winawer SJ, Shike M. Dietary factors in colorectal cancer and their possible effects on earlier stages of hyperproliferation and adenoma formation. J Natl Cancer Inst 1992;84:74-5.
[26] Winters MD, Schlinke TL, Joyce WA, Glore SR, Huycke MM. Prospective case-cohort study of intestinal colonization with enterococci that produce extracellular superoxide and the risk for colorectal adenomas or cancer. Am J Gastroenterol 1998;93:2491-500.
[27] Hemminki K, Chen B. Familial risk for colorectal cancers are mainly due to heritable causes. Cancer Epidemiol Biomarkers Prev 2004;13:1253-6.
[28] Marchand LL. Combined influence of genetic and dietary factors on colorectal cancer incidence in Japanese Americans. J Natl Cancer Inst Monogr 1999;101-5.
[29] Lichtenstein GR. Reduction of colorectal cancer risk in patients with Crohn's disease. Rev Gastroenterol Disord 2002;2:S16-S24.
[30] Riegler G, Carratu R, Tartaglione M, Morace F, Manzione R, Arimoli A. Prevalence and relative risk of malignancy in relatives of inflammatory bowel disease patients and control subjects. J Clin Gastroenterol 1998;27:211-4.
[31] Jain SK, Peppercorn MA. Inflammatory bowel disease and colon cancer: a review. Dig Dis 1997;15:243-52.
[32] Itzkowitz SH. Inflammatory bowel disease and cancer. Gastroenterol Clin North Am 1997;26:129-39.
[33] Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287:G7-17.
[34] Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends Mol Med 2002;8:10-6.
[35] Bussey HJR. Historical developments in familial polyposis. In: Herrera L, editor. Familial adenomatous polyposis. New York (NY): Alan R. Liss; 1990. p. 1-7.
[36] Peltomaki P, De la Chapelle A. Mutations predisposing to hereditary nonpolyposis colorectal cancer. Adv Cancer Res 1997;71:93-119.
[37] Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, et al. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 1993;104:1535-49.
[38] Bonita R, Howe AL. Older women in an aging world: achieving health across the life course. World Health Stat Q 1996;49:134-41.
[39] Prior TW, Chadwick RB, Papp AC, Arcot AN, Isa AM, Pearl DK, et al. The I1307K polymorphism of the APC gene in colorectal cancer. Gastroenterology 1999;116:58-63.
[40] Rozen P, Shomrat R, Strul H, Naiman T, Karminsky N, Legum C, et al. Prevalence of the I1307K APC gene variant in Israeli Jews of differing ethnic origin and risk for colorectal cancer. Gastroenterology 1999;116:54-7.
[41] Menges M, Gartner B, Georg T, Fischinger J, Zeitz M. Cost-benefit analysis of screening colonoscopy in 40- to 50-year-old first-degree relatives of patients with colorectal cancer. Int J Colorectal Dis 2005;[Epub]:1-6.
[42] Lindberg J, Stenling R, Palmqvist R, Rutegard J. Efficiency of colorectal cancer surveillance in patients with ulcerative colitis: 26 years' experience in a patient cohort from a defined population area. Scand J Gastroenterol 2005;40:1076-80.
[43] Losi L, Di Gregorio C, Pedroni M, Ponti G, Roncucci L, Scarselli A, et al. Molecular genetic alterations and clinical features in early-onset colorectal carcinomas and their role for the recognition of hereditary cancer syndromes. Am J Gastroenterol 2005;100:2280-7.
[44] Hakama M, Hoff G, Kronborg O, Pahlman L. Screening for colorectal cancer. Acta Oncol 2005;44:425-39.

[45] Janssens JF. Faecal occult blood test as a screening test for colorectal cancer. Acta Gastroenterol Belg 2005;68:244-6.
[46] Yang SH, Chien CC, Chen CW, Li SY, Huang CJ. Potential of faecal RNA in diagnosing colorectal cancer. Cancer Lett 2005;226:55-63.
[47] Janssens JF. Flexible sigmoidoscopy as a screening test for colorectal cancer. Acta Gastroenterol Belg 2005;68:248-9.
[48] Atkin W. Options for screening for colorectal cancer. Scand J Gastroenterol Suppl 2003;13-6.
[49] Ouyang DL, Chen JJ, Getzenberg RH, Schoen RE. Noninvasive testing for colorectal cancer: a review. Am J Gastroenterol 2005;100:1393-403.
[50] Bromer MQ, Weinberg DS. Screening for colorectal cancer – now and the near future. Semin Oncol 2005;32:3-10.
[51] Autier P, Boyle P, Buyse M, Bleiberg H. Is FOB screening really the answer for lowering mortality in colorectal cancer? Recent Results Cancer Res 2003;163:254-63.
[52] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence. Mortality and prevalence worldwide. IARC cancer base no. 5, version 2.0. Lyon (France): IARC Press; 2004.
[53] Slater G, Papatestas AE, Tartter PI, Mulvihill M, Aufses AH, Jr. Age distribution of right- and left-sided colorectal cancers. Am J Gastroenterol 1982;77:63-6.
[54] Vobecky J, Leduc C, Devroede G. Sex differences in the changing anatomic distribution of colorectal carcinoma. Cancer 1984;54:3065-9.
[55] Jensen OM. Different age and sex relationship for cancer of subsites of the large bowel. Br J Cancer 1984;50:825-9.
[56] Schub R, Steinheber FU. Rightward shift of colon cancer. A feature of the aging gut. J Clin Gastroenterol 1986;8:630-4.
[57] Jass JR. Subsite distribution and incidence of colorectal cancer in New Zealand, 1974-1983. Dis Colon Rectum 1991;34:56-9.
[58] Kee F, Wilson RH, Gilliland R, Sloan JM, Rowlands BJ, Moorehead RJ. Changing site distribution of colorectal cancer. BMJ 1992;305:158.
[59] Demers RY, Severson RK, Schottenfeld D, Lazar L. Incidence of colorectal adenocarcinoma by anatomic subsite. An epidemiologic study of time trends and racial differences in the Detroit, Michigan area. Cancer 1997;79:441-7.
[60] Ji BT, Devesa SS, Chow WH, Jin F, Gao YT. Colorectal cancer incidence trends by subsite in urban Shanghai, 1972-1994. Cancer Epidemiol Biomarkers Prev 1998;7:661-6.
[61] Bonithon-Kopp C, Benhamiche AM. Are there several colorectal cancers? Epidemiological data. Eur J Cancer Prev 1999;8:S3-12.
[62] Troisi RJ, Freedman AN, Devesa SS. Incidence of colorectal carcinoma in the U.S.: an update of trends by gender, race, age, subsite, and stage, 1975-1994. Cancer 1999;85:1670-6.
[63] Miller A, Gorska M, Bassett M. Proximal shift of colorectal cancer in the Australian Capital Territory over 20 years. Aust N Z J Med 2000;30:221-5.
[64] Mitry E, Benhamiche AM, Couillault C, Roy P, Faivre-Finn C, Clinard F, et al. Effect of age, period of diagnosis and birth cohort on large bowel cancer incidence in a well-defined French population, 1976-1995. Eur J Cancer Prev 2002;11:529-34.
[65] Cucino C, Buchner AM, Sonnenberg A. Continued rightward shift of colorectal cancer. Dis Colon Rectum 2002;45:1035-40.
[66] Takada H, Ohsawa T, Iwamoto S, Yoshida R, Nakano M, Imada S, et al. Changing site distribution of colorectal cancer in Japan. Dis Colon Rectum 2002;45:1249-54.
[67] Thygesen LC, Gronbaek M, Johansen C. Colorectal cancer in Denmark 1943-1997. Dis Colon Rectum 2004;47:1232-41.
[68] Rabeneck L, Davila JA, El Serag HB. Is there a true "shift" to the right colon in the incidence of colorectal cancer? Am J Gastroenterol 2003;98:1400-9.
[69] White JS, McCallion K, Gardiner KR, Watson RG, Collins JS, McKee F, et al. Changing patterns of colorectal cancer. Am J Gastroenterol 2004;99:766.
[70] Ministry of Health. Israel National Cancer Registry. 2005. Available at: http://www.health.gov.il/icr/. [Last Accessed: 1/06].
[71] Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169-74.
[72] Maddox M. Older women and the meaning of health. J Gerontol Nurs 1999;25:26-33.
[73] Parkin DM, Whelan SL, Ferlay J, Teppo L, editors. Cancer incidence in five continents, volume VIII. IARC Scientific Publication No. 155. Lyon (France): International Agency for Research on Cancer; 2002.
[74] The World Bank. Data & statistics: country classification. 2006. Available at: http://www.worldbank.org/data/countryclass/classgroups.htm. [Last Accessed: 1/06].