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The changing incidence and sites of colorectal cancer in the Israeli Arab population and their clinical implications

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Israeli Arabs have been at low risk for colorectal cancer (CRC) and had mainly proximal cancer, but increasing CRC is now noted. We examined this trend and CRC site and compared them to the total Jewish population and to the low-risk Jews of Asian-African origin. Israel Cancer Registry CRC data, 1982–2002, for Arabs and Jews was computed by gender, age and site: rectal cancer included recto-sigmoid junction; ''right-sided'' CRC included the proximal colon up to and also the splenic flexure. During 1982–2002, Arab CRC trends increased significantly in both sexes due to *left*-sided CRC (women, $p = 0.01$; men, $p = 0.02$) and rectal cancers ($p = 0.05$). *Left*-sided CRC increased significantly in both men and women aged $\geq$ 65 years ($p = 0.02$). Comparing 1982–1984 to 2000–2002, the proportion of right-sided CRC decreased in both genders ($p < 0.01$) from 39.4 to 27.1% of male CRC, and from 44.8 to 31.3% in females. In general, this pattern of increasing rectal and left-sided CRC had been seen over a decade earlier in Jews of Asian-African origin and then their trend reversed during the last decade. In conclusion, there is a recent trend for left-sided CRC in Israeli Arabs, probably related to their changing life style. These results should influence their cancer preventive lifestyle recommendations, and CRC screening and diagnostic methodologies used.

Key words: Arabs; cancer site; colorectal cancer; Israel; Jews

In Israel, approximately 3,000 new cases of colorectal cancer (CRC) are being diagnosed annually, representing 13% of all new cancer cases. Notably, Jews of European origin have been at highest risk for CRC as compared to non-European Jews, and non-Jews being at the lowest risk. This is attributed to different genetic susceptibility and/or lifestyle and diet.[1–3]

The most common diseases causing mortality in Israeli Arabs are now heart diseases (19%) and cancer (17%), while in Jews, cancer caused 24% of their mortality (figures not age-adjusted).[4,5] CRC was uncommon in the Israeli–Arab population, however, there has been a recent change in its incidence.[6,7] It is now the second most common malignancy in Arab women and third in men. This was due to an increase in CRC from 1982 to 2002, of 138% in men and 205% in women, as compared to the rise of 17% in the Jewish population.[3,7] In the past, right-sided CRC was prominent in the Arab population.[6] However, recently there is clinical evidence of increasing left-sided CRC.[8]

The aims of this study were to follow Israeli Arab long-term CRC incidence trends by anatomic site, sex and age group and compare them with the Jewish population. The goal was to evaluate the clinical implications of the findings and possible treatable risk-factors.

Material and methods

Israeli Arab population

Since establishment of Israel in 1948, the Arab population increased due to low infant mortality and longer life expectancy, from 156,000 persons to 1.2 million (18.5% of the population) in 2002.[4,9] Most (71%) live in Arab localities and 29% live in mixed Arab–Jewish cities. Health insurance is compulsory for all citizens and health services are uniform and regional, independent of ethnicity.[4,9]

Just as the Israeli Jewish population is ethnically heterogeneous, so are the Arab citizens classified into 4 major groups who for religious and extended family reasons maintain separate identities and areas of residency. The majority, 82%, are Sunni Moslems, who over centuries migrated from neighboring countries or brought by invading forces. The Druze are a separate ethnic group (9%) residing in the mountainous areas, and the Bedouin are a nomadic people from the Arabian Peninsula. The fourth major group is the Christian Arabs (9%) who are also heterogeneous, derived from divisions of the Christian Church.[4,10]

Many had also admixed with invading forces and indigenous inhabitants, as illustrated by finding in some Arabs of the ancient *APC* I1307 variant occurring mainly in Ashkenazi Jews.[2,11,12] It has been traditional to marry within the extended family and so the potential for familial cancer susceptibility is increased in some of these extended families.[4,5,8]

Cancer patients and data

This included all CRCs that were diagnosed in Arab citizens from 1982 to 2002. The data source is the Israel National Cancer Registry (INCR) and its description has been published in detail.[3] In summary, the INCR is a population-based central tumor registry established in 1960 and since 1982 reporting to the registry is mandatory.[7] All medical facilities, both public and private and pathology laboratories that are diagnosing or treating cancer patients send a copy of their medical summary to the Registry. The INCR also collects data on cancer deaths from District Health Authorities and the Central Population Registry.

In Israel, everyone receives at birth, or immigrants upon getting citizenship, a personal identification number (PID). This PID identifies an individual in all his/her contacts with all organizations in the country, including the health system. All demographic data, including place of birth and immigration date, as well as residential and other personal data (including religion) are stored in the Central Population Registry. The INCR is linked to this Registry and each cancer patient's personal data are then retrieved and validated. The last audit of data completeness concluded that registration was above 95%.[13]

In the INCR, in addition to demographic data, all data available on the CRC is registered including date of diagnosis and tumor location using the International Classification of Diseases, Oncology (ICD-O) version-3 codes.[14]

Abbreviations: ASR, age-standardized rate; CRC, colorectal cancer; ICD-O, International Classification of Diseases, Oncology; INCR, Israel National Cancer Registry; PID, personal identification number; RR, relative risk; SEER, Surveillance, Epidemiology and End Results program (USA).

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TABLE I – MEAN AGE STANDARDIZED INCIDENCE RATES (ASR)/10^5, 2000–2002, FOR COLORECTAL CANCER, COLON AND RECTAL CANCERS AND THEIR RELATIVE RATE RATIOS (RRR) IN ARABS AND JEWS, AND BY GENDER (REF. 7)

Population	All colorectal cancer	Colon cancer	Rectal cancer	RRR	*p* vs.* Arabs
All Arabs	16.9	11.3	5.6	2.0	
All Jews	37.4	26.7	10.7	2.5	<0.01
Jews, Asian-African	29.2	20.7	8.5	2.4	<0.01
Males					
Arabs	17.3	10.5	6.9	1.5	
Jews, all	41.2	28.7	12.5	2.3	<0.01
Jews, Asian-African	31.0	21.9	9.2	2.4	<0.01
Females					
Arabs	16.9	12.3	4.5	2.7	
Jews, all	32.9	24.1	8.8	2.8	NS
Jews, Asian-African	27.1	19.1	8.1	2.4	0.01

*Age-adjusted comparisons of Jews and Arabs.

TABLE II – NUMBERS OF COLORECTAL CANCER PATIENTS AND RATES/10^5, 1998–2002, FOR COLORECTAL, COLON AND RECTAL CANCERS IN ARABS AND JEWS, AND BY GENDER (REF. 7)

Population	All colorectal cancer		Colon cancer		Rectal cancer	
	No.	Rate/10^5	No.	Rate/10^5	No.	Rate/10^5
All Arabs	329	26.41	242	19.43	87	6.98
All Jews	9081	170.56*	7214	135.49	1867	35.07
Jews, Asian-African	2019	128.78*	1554	99.12	465	29.66
Males						
Arabs	157	24.77	107	16.88	50	7.89
Jews, all	4530	173.70*	3533	135.47	997	38.23
Jews, Asian-African	1049	135.90*	786	101.83	263	34.07
Females						
Arabs	172	28.11	135	22.06	37	6.05
Jews, all	4551	167.54*	3681	135.52	870	32.03
Jews, Asian-African	970	121.87*	768	96.49	202	25.38

*p *versus* Arabs, <0.01.

Statistical methods

Age-standardized incidence rates (ASR) were computed per 10^5 populations, standardized to ''World Standard Population.'' Rates were computed for each large bowel site. Israeli population data, by age group and gender, were retrieved from the Central Bureau of Statistics.[9] Trend analysis was computed by linear regression. Tests of significance used confidence intervals of 95% and a significant result was when $p < 0.05$.

Evaluations for CRC in Arabs and Jews were made by gender, cancer site and age groups. For sites, we analyzed rectal cancer (ICD-O codes C20.9, 20.9a), including rectosigmoid junction (C19.9), but not anal cancer, *vs.* the remaining large bowel. For ''right-sided'' CRC we evaluated from C18.0 (cecum) to and including C18.5 (splenic flexure), but excluded appendix. For ''left-sided'' CRC we included the remainder of the large bowel sites from C18.6 to C20.9a, including rectum but excluding anal cancer. Because of the relatively small numbers of Arab CRC, we grouped the cases as all ages, as well as <65 years old or ≥65 years old. The relative proportions of colon *vs.* rectal CRC incidence were compared for 5-year period from 1982 to 2002, with age-adjustment when comparing rate ratios. We also compared these results with the total Israeli Jewish CRC population and with Israeli Jews of African–Asian origin as they had been the Jewish group at lowest-risk for CRC.[15,16] Because of the relatively small numbers of Arab CRC, incidence data is presented as all CRC occurring from 1998 to 2002.

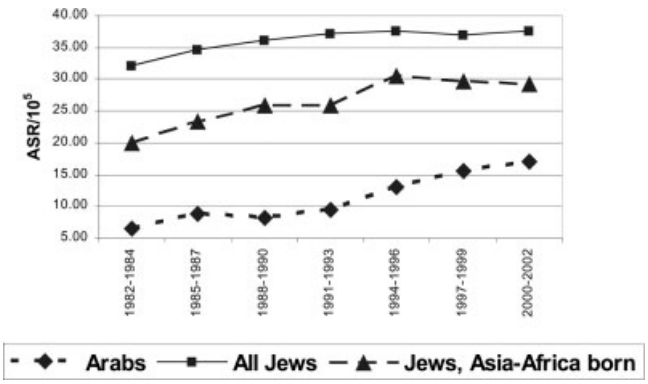

FIGURE 1 – Incidence trends of CRC from 1982 to 2002 in Arabs, all Jews and Asia-Africa-born Jews. In Arabs, the incidence is significantly increasing mainly in the last decade ($p < 0.01$). In the total Jewish population, the incidence initially also rose significantly, but less steeply, and has remained at a higher, but stable plateau ($p = 0.01$). In Asia-Africa-born Jews, CRC incidence is intermediate between the two, and had also been consistently increasing significantly ($p < 0.01$), but now at a plateau level during the last decade.

Results

Population studied

Out of 1,207 Arab CRC patients who entered into the analysis, there were 612 men (50.7%) and 595 women; 696 with left-sided CRC and 321 right-sided. Rectal cancer occurred in 428 (35%), 232 men and 196 women. Details on the total Jewish CRC population and comparison Jewish Asian–African ethnic group are available elsewhere.[3] The recent CRC incidence age standardized rates (ASR) and by site, for Arabs and Jews, during 1998–2002, are given in Tables I and II.

Incidence trends, 1982–2002, for colorectal, colon and rectal cancers for the Arab population and by gender, and comparisons with the Jewish population

From 1982 to 2002, the overall incidence trends of Arab CRC were of a steady increase in women and a later but greater increase in men ($p < 0.01$ for both) (Fig. 1). Overall, the mean CRC ASR of Arabs 1982–1984 *vs.* 2000–2002 increased 138% in males and

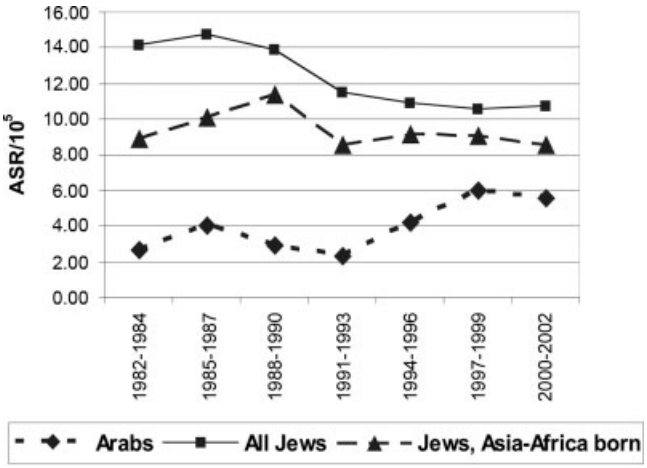

FIGURE 2 – Incidence trends of rectal cancers from 1982 to 2002 in Arabs, all Jews and Asia-Africa-born Jews. In Arabs, rectal cancer incidence has been rising ($p = 0.05$) and now at a plateau level. In the total Jewish population, there was a decreasing incidence ($p < 0.01$) and since the last decade is at a plateau level. In Asia-Africa-born Jews, rectal cancer incidence is intermediate between the other two, and trends were on an initial rise a decade earlier than that of the Arabs to almost reach the higher incidence of the total Jewish population, and since then remained at a lower plateau level.

205% in females. Colon cancer rates increased significantly in all Arabs ($p < 0.01$), mainly in females ($p < 0.01$) and less so in males ($p = 0.05$) (Table II). Arab rectal cancer rates, 1982–1984 *vs.* 2000–2002, rose 165% in men and 69% in women (Fig. 2).

In the total Jewish CRC population and by gender, their incidence parameters were higher than those of the Arab population, but lately at a plateau level (Figs. 1 and 2). However, while the incidence of rectal cancer was decreasing in the Jewish population ($p < 0.01$), it was increasing in the Arab population ($p = 0.05$) (Fig. 2).

Comparing Arab CRC trends with those of Asian–African origin Jews, the increasing incidence trends of the later were higher, but for the last decade are at a plateau level paralleling those of the total Jewish population (Fig. 1). However, while they initially had a rising incidence of rectal cancer until the last decade and a plateau since then, the incidence of rectal cancer in Arabs rose from that time to plateau at a lower level (Fig. 2).

The relative rate ratios of colon to rectal cancers are now significantly lower in the Arab CRC population as compared to CRC in all the Jews and also to Asian–African Jews, who have an intermediate level (Table I).

Incidence trends 1982–2002 by age groups, ethnic groups and gender

In the <65 years of age, there was a nonsignificant increased trend for CRC in male Arabs and Jews of Asian–African origin. But the trend for increasing CRC incidence in women from these two ethnic groups was significant ($p = 0.01$ and 0.03, respectively). In the ≥65 years of age, the increased CRC trend in males was significant for Arabs ($p = 0.01$) and Jews of Asian–African origin ($p = 0.03$). While in females, the increased trend was not statistically significant in either ethnic group.

Incidence trends, 1982–2002, for left and right-sided CRC by ethnic group, age group and gender

Overall, there were trends for increased left-sided CRC in Arab men and women of all ages ($p = 0.01$) and those aged ≥65 years ($p = 0.02$), while those trends in Jews were stable (Fig. 3). Conversely, the right-sided CRC trends in Arabs were stable, but increased significantly in Jews aged ≥65 years, $p = 0.02$ for men and 0.01 for women.

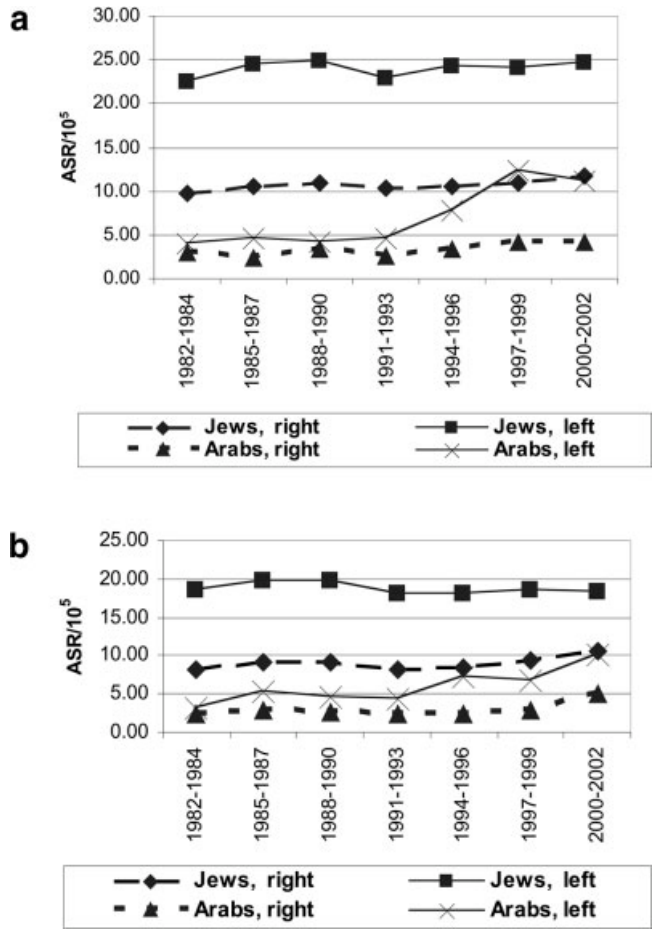

FIGURE 3 – Right and left-sided CRC incidence trends from 1982 to 2002 in Arabs and Jews of all ages (*a*) males (*b*) females. In Arabs, the incidence of right-sided CRC rose insignificantly in both genders, while left-sided CRC increased significantly in men ($p = 0.02$) and women ($p = 0.01$). In contrast, the incidences trends of left-sided CRC in Jews were stable, but at a higher level, while right-sided CRC levels were also higher with a rising trend in women.

Quantifying the shift to left-sided CRC in the Arab population

Comparing 1982–1984 to 2000–2002, the relative rate ratio between CRC incidence rates for left *vs.* right-sided, for the entire population and by gender, are summarized in Table III. In all Arabs, men and women, there was a significantly increased risk for left CRC ($p < 0.01$) and the rate ratio for left-sided CRC increased significantly ($p < 0.01$). In contrast, in the Jewish population, in the period 1998–2002, the rate ratios decreased in all, least in African–Asian-born Jews, but decreased significantly in Jewish women, because of their increased proportion of right-sided CRC. These rate ratios in the Jewish population were significantly different from those of the Arab population ($p < 0.01$) (Table III).

In the time period 1982–1984, there were only 63 CRC cases in Arabs, of these, 35 were in men and 28 in women. Right CRC occurred in 41.3%, representing 37.1% of all CRC in males and 46.4% in females. In the period 2000–2002, there were 315 CRC cases, of these 149 were in men and 166 in women. The proportion of right CRC decreased to 26.3% of all CRC, representing 24.2% of all the CRC in males (NS), but 28.3% of CRC in females ($p < 0.01$).

Discussion

This long-term national analysis of CRC confirmed a recent significant progressive increase in the amount of rectal and left-sided

TABLE III – MEAN AGE STANDARDIZED INCIDENCE RATES (ASR)/10^5 FOR LEFT AND RIGHT COLORECTAL CANCER (CRC), AND THEIR RELATIVE RATE RATIOS (RRR) 1982–1984 *VERSUS* 2000–2002 IN ARABS AND JEWS, AND BY GENDER, AND SIGNIFICANCE OF THEIR RELATIVE CHANGES

Population	1982–1984			2000–2002			*P* change	*p* vs.* Arabs
	ASR		RRR	ASR		RRR		
	Left CRC	Right CRC		Left CRC	Right CRC			
Arabs, all	3.51	2.68	1.31	10.62	3.65	2.91	<0.01	
Jews, all	20.22	8.97	2.26	21.45	11.16	1.92	NS	<0.01
Jews, Asian-African	16.30	6.26	2.15	16.30	7.57	2.15	NS	0.01
Males								
Arabs	3.89	3.04	1.28	11.06	4.17	2.65	<0.01	
Jews, all	22.04	9.75	2.26	24.70	11.81	2.09	NS	<0.01
Jews, Asian-African	14.75	6.26	2.36	17.77	7.71	2.30	NS	<0.01
Females								
Arabs	3.89	2.90	1.34	7.77	3.62	2.15	<0.01	
Jews, all	19.28	8.84	2.18	18.62	9.68	1.92	0.04	0.05
Jews, Asian-African	12.08	4.51	2.58	16.09	7.87	2.04	<0.01	NS

*Age-adjusted comparisons of Arabs and Jews. Right-sided includes cecum up to and including splenic flexure. Left-sided includes the remaining colorectum.

CRC in the Israeli Arab population.[8] This trend is different from that now seen in Israeli Jewish ethnic groups.

Israeli-Jews, especially males, from Europe or Americas are at highest risk for CRC as compared to other Jewish populations.[1,15] The markedly rising incidence in Jews born in Asia or Africa, who were the population at lowest risk, was initially rectal and then left-sided CRC, and is consistent with the effects of long-term diet and lifestyle, namely ''westernization'' and associated affluence of a Mediterranean and Middle Eastern people.[16] This pattern was seen in other immigrants moving from low-risk for CRC countries, such as southern Italy or Greece, to high-risk for CRC countries such as the United States or Australia.[1,17]

Israel-born Jewish CRC patients now have the lowest CRC incidence of all Jewish groups.[3,7] They are increasingly the descendants of inter-ethnic marriages and so have a merging of the diet and lifestyle of those ethnic groups as well as their genetic characteristics.[2,9] This is in contrast to the Israeli Arab groups who marry within their own community and frequently, in 44%, to their extended family members.[4,18,19] This is, unfortunately, illustrated by their high incidence of congenital malformations and disorders, and has contributed to the finding of micro-satellite instability in a high proportion of CRC patients from a defined area.[4,12,18] In another defined area, Arabs with CRC were significantly younger in age and their pathology was more likely to be poorly-differentiated and mucinous than CRC in Jewish patients.[20] This issue of consanguinity is now being intensively addressed by education of the youth at risk.[4,19]

The temporal pattern of CRC site incidence trends in industrialized and ''westernized'' countries is that of a decreasing incidence of rectal cancer and an increase in proximal colon cancer.[17] This has been noted worldwide in diverse populations.[21–29] In our Jewish population, over the last 3 decades we had observed a pattern of an initial increase in rectal cancer incidence in the lowest-risk population of Asian-African origin, followed by a decreasing incidence both in them and the high-risk European Jews. There is now a merged plateau incidence level of all long-term immigrant groups and Israel-born.[3]

Initially, right-sided CRC had been prominent in Israeli Arabs, consistent with observations made in other Arab populations, and was likely partially explained by unrecognized genetic risk factors.[6] The CRC incidence pattern in Israeli Arabs is now similar to what we had observed in the Israeli Jews of Asian–African origin, but occurring a decade later. This rising incidence is not attributed to screening, as CRC screening in Arabs even though available through compulsory health insurance, is not used, less so than is mammography screening (overall uptake of CRC screening in Israel is 21%, mammography uptake being 55–60% in Jewish women and 40–45% in Arab women, Dr. G. Rennert, Carmel Hospital, Haifa). Nor is the changing incidence due to a difference of health care as this is regional and uniformly available. The reasons for the changing Arab CRC incidence and site are assumed related to their changing diet and lifestyle associated with industrialization and increasing affluence.[30,31] Israeli Arabs have become more educated, affluent, urbanized, less likely to work in agriculture and few Arab women work outside home.[4] Arab men smoke more tobacco than Jewish men; diabetes is more common in Arabs than in Jews, Arab women are almost twice as likely to be obese than Jewish women, myocardial infarction is almost twice as common.[4,5] These are all CRC risk factors associated with industrialization and affluence.[32]

There is relatively little published CRC epidemiological data from adjacent Arab-Middle Eastern countries. There are hospital-based series that describe proximal CRC occurring in young-aged patients, sometimes with a family history of cancer.[33–38] They too emphasize the higher rates of consanguineous marriage in their communities and the finding of hereditary nonpolyposis CRC in a proportion of patients.[12,38–40] The most complete published data is from the Kingdom of Jordan and confirms the higher risk for rectal cancer in their population as compared to SEER or Israeli data.[41] A Middle East Consortium monograph, comparing malignant diseases in 5 Middle Eastern populations, 1996–2002, is now being published by the National Cancer Institute (USA). This will provide more comparative data from neighboring countries.

Primary prevention also requires understanding the genetic risk of intrafamilial marriage and this understanding has improved in Israeli Arab high-school children.[19] However, it is difficult to obtain consent for genetic consultation and testing in their conservative older generation, sensitive to the possibility of genetic discrimination for arranged marriages. So, their genetic susceptibility for CRC is only now being evaluated. The public education on avoiding tobacco smoking and obesity and the need for preventive medical examinations for cancer and heart disease have not made the same impression on the conservative Arab community as it has on the Jewish public. This will require a more dedicated and Arab-oriented education program.[19]

In conclusion, in Israeli Arabs, there is an increasing incidence of CRC, especially in women. The proportion of right-sided CRC has decreased significantly, and rectal and left-sided cancer increased, especially in men. Colorectal screening and diagnostic methodologies in this population must address this clinical problem, and genetic consultation and education on primary prevention and screening need to be emphasized.

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