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Trends in colorectal cancer incidence and mortality in the Israeli Jewish ethnic populations

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Key words: Ashkenazi, colorectal cancer, incidence, Jews, Sephardi, survival

Abstract

Background: Ashkenazi Jews, as compared to non-European Jews and non-Jews, are at increased risk for colorectal cancer (CRC), this is attributed to genetic susceptibility and/or lifestyle. *Aims:* To follow Israeli long-term trends in CRC incidence and mortality and their associations with ethnicity. *Methods:* All Israeli CRC data accumulated 1970–2001 was used, age standardized rates (adjusted to world standard population) was computed by cancer site, US Surveillance, Epidemiology and End Results Program (SEER) Stage and ethnic group (continent of birth: Europe–America, Asia, Africa, Israel). *Results:* From 1970, CRC *incidence* increased 190% in males and 140% in females; mainly colon cancer (270% and 185% respectively) ($P < 0.01$), while rectal cancer incidence decreased and is now stable. Stage 3 CRC increased while stage 4 decreased significantly ($P < 0.01$ for both). In 2001, CRC incidence per 100,000 in European–American-born males was 48.3, Asian and African born 35.5 and Israeli born 32.7 (relative risk (RR) 1.36, $P = 0.03$), while European–American female rates were 35 and all the others 26 (RR 1.35, $P < 0.01$). Overall *survival* increased 9% over 30 years ($P < 0.01$), 5 years survival since 1988–1996 for European–American born was 43.1%, Asian 46.7%, African 47.5% and Israeli 55.8%. Stage-2 CRC 5 years survivals for 1970–1996 (most had no post surgical treatment) for European–American born were 41.7%, Asian and African 44.8% and Israeli 53.4% ($P < 0.05$). Stage-3 CRC survivals (most received adjuvant therapy in addition to surgery) for European–American born was 38.8%, Asian and African 43.3% and Israeli 45.1% ($P < 0.01$). *Conclusions:* Colon cancer has increased in Israel, mainly in males and European–American born. Israeli-born Jews (of 20 to 60% mixed ethnicity and lifestyle habits) have the lowest incidence and best survival data for stages-2 and -3 CRC. There is evidence of ethnic survival advantage and possibly in response to adjuvant oncological therapy.

Abbreviations: ASR – age-standardized rate; CRC – colorectal cancer; FSU – former Soviet Union; INCR – Israel National Cancer Registry; PID – personal identification number; RR – relative risk; SEER – US Surveillance, Epidemiology and End Results Program

Introduction

Colorectal cancers (CRC) rank second in the total number of cancer cases diagnosed annually both in Israeli males and females. Approximately 3000 new cases are being diagnosed annually in Israel, representing 13% of all new cancer cases. From the epidemiological point of view CRC is divided into two sites – colon and rectal cancers. Although these two malignancies share several etiological factors as well as treatment modalities, they differ markedly in morbidity trends. Historically, Ashkenazi (European) Jews, as compared to non-European Jews and non-Jews, have been noted to be at increased risk for CRC, this is attributed to different genetic susceptibility and/or lifestyle and diet [1–5]. The aims of this study were to follow Israeli long-term trends in CRC incidence and mortality and their associations with ethnicity. Data are presented for both colon and rectal malignancies together, or separately according to its relevance to the parameter examined.

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Materials and methods

Cancer patients and data

This included all CRCs that were diagnosed in Jewish citizens residing in the State of Israel from 1970 to 2001. The data source is the Israel National Cancer Registry (INCR), a population-based central tumor registry that was established in 1960 and is in operation since then [6]. Since 1982, reporting to the registry is mandatory and includes all medical facilities in the country, both public and private. Regardless of their ownership, all medical institutions and pathology laboratories that are diagnosing or treating cancer patients, report to the registry by sending a copy of the medical summary (including pathology and cancer stage) that states that a person has or had a notifiable disease. The INCR also collects data on cancer deaths from District Health Authorities and the Central Population Register. In Israel, every newborn receives at birth a personal identification number (PID), the same occurs for new immigrants upon getting citizenship. This PID serves for identifying a certain person from birth to death in all his 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 the population registry via computerized systems and each cancer patient's personal data are validated and retrieved from the population registry. In addition to demographic data, all data available on the CRC is registered in the INCR. These include: date and place of diagnosis, detailed tumor location (using the ICDO-3 codes), histopathology type, stage at time of diagnosis, tumor size, lymph nodes involved and information on treatments in the first 6 months after diagnosis [7].

Completeness of data

The registry has been in operation since 1960. From 1960 to 1982 reporting to the registry was on voluntary basis, nevertheless, reporting was at a very high level. In 1982 a Governmental decree obliged all Medical Institutions to report on their cancer patients and established a set of rules on how and when reports should be sent. During the 43 years of INCR existence audits were made of the data completeness. The last published in 2003 was of 1991 data and concluded that completeness of registration was above 95% [8]. Since that survey several measures were taken to improve completeness and accuracy of reporting, including annual courses for Medical Registrars and other workers at the Cancer/Medical Institutes on reporting and cancer registration.

Israeli population

The State of Israel was established in 1948. At that time the Jewish population in Israel counted about 650,000 people and a massive wave of immigration came first from Jews surviving the holocaust in Europe and later on, in the early 1950s, from Arab and other Muslim countries in the Maghreb (North Africa) and Asia. The Arab population in Israel was about 150,000, 25% of the entire population in 1949. In the latest National Statistical Report of 2001 the Israeli population comprised 6.5 million people, 19% Arabs and most of the rest (5 million) Jews [9]. In 2001, 41% of the entire population were immigrants and the remainder were Israeli born. The Jewish population then comprised 62% Israeli born. The median age of the entire population was 27.7 years, 30 years in Jews and 19.9 in Arabs. Within the Jewish population the major ethnic groups are usually defined by the place of birth of each person (and also for epidemiological studies) and these are grouped into four categories: those who were born in Europe or America (Austria, Bulgaria, Czech Republic, Germany, Greece, Hungary, North America, northern Europe, Poland, Romania, Slovakia, South America, former USSR, western Europe); Asia (India, Iran, Iraq, Lebanon, Syria, Turkey, Yemen); Africa (Algeria, Egypt, Ethiopia, Libya, Morocco, Tunisia), and those who were born in Israel [9]. This geographic subdivision corresponds only approximately to ethnic groups usually defined as 'Ashkenazim' (those who were born in Europe and America) and 'Sephardim' (those who were born in Asia and Africa). As described elsewhere, historically, there was geographic intermingling of Jewish ethnic groups [10]. Of those who were born outside Israel, 72% were born in Europe or America (assumed to be 'Ashkenazi' Jews), 16% in African countries and 12% in Asia [9]. Because of their relatively small numbers, the statistics of the latter two groups are usually added together in order to compare them with the 'Ashkenazi' majority.

Statistical methods

Age-standardized rates (ASR) were computed per 100,000 populations, standardized to the 'World Standard Population'. Rates were computed for each site and sub-site and 'ethnic' group (country/continent of birth). The 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 $P < 0.05$. For CRC stage definition we used the SEER (US Surveillance, Epidemiology and End Results Program) criteria where stage 1 indicates localized disease, stage 2 is for disease spreading regionally, stage 3 is disease spread to lymph nodes and stage 4 denotes distant metastasis [7]. We combined the *in-situ* cases to stage 1 due to their scarcity of cases. Absolute survival rate was calculated for each ethnic group, CRC

stage at time of diagnosis and time period. Calculations were made separately for those who were diagnosed in the period 1970–1978, 1979–1987 and 1988–1996, or their combination, with a follow-up till the end of year 2000.

Results

Incidence trends

From 1970 to 2001, the overall incidence trends of colon cancer were of a sharp and steady increase all along the time period (Figure 1). The age adjusted Jewish CRC rates increased 190% in males and 140% in females (Figures 2a and b). The increase was mainly of colon cancer (270% and 185%, respectively) ($P < 0.01$) (Figures 3a and b). The rectal cancer trends showed a rise in rates from 1970 to mid-1980s, giving an increase of 180% in men and 130% in women. Thereafter, a decrease in incidence in both sexes occurred until the late 1990s, 25% in men and 30% in women, with little variation since then (Figures 4a and b).

Incidence by ethnic group

Out of 38,493 CRC patients who were entered into the analysis 72.5% were born in Europe–America, 10% in Asia, 8% in Africa and 9.5% in Israel (Table 1). The proportion of each ethnic group at each CRC stage remained constant. However, over the 3 time periods analyzed, the proportion of African–Asian CRC patients increased from 13.9% in 1970–1978 to 17.9% and then to 20.4% in 1980–1996. The proportion of Israeli born increased from 5.4% to 7.2% and then to 8.2%. Conversely, the proportion of European–American born Jews decreased from 80.7% to 74.9% and then to 70.8% in the last time period ($P < 0.01$ for all).

For Jewish males, the highest CRC incidence rates in 2001 were noted in the Europe–America born (48.3 out of 100,000), followed by those born in Asia or Africa (35.5 out of 100,000 on average in 1999–2001) and those born in Israel (32.7 out of 100,000 in 2001) giving European–American born RR of 1.36, $P = 0.03$ (Figure 2a). In 2001, in Jewish females the highest rate of 35 out of 100,000 was observed in those who were born in Europe–America, and all the other groups had rates of 26 out of 100,000 (on average in 1999–2001) (RR 1.35, $P < 0.01$) (Figure 2b). Examining colon and rectal cancers separately, there were the same patterns in men and women for colon cancer (Figures 3a and b), but a slightly different one for rectal cancer. Male incidence rates for rectal cancer were 13 out of 100,000 both for Jews from Africa and Europe–America. While those who were born in Israel had a rate of 10 out of 100,000 (on average) and Jews from Asia had a rate of 8 out of 100,000. In women, the rectal cancer incidence of all ethnic groups converged and European–American born were 9 out of 100,000, while African–Asian and Israeli born were 8 out of 100,000 (Figures 4a and b).

Incidence trends by cancer stage and sex

The data are presented for three periods from 1970 to 1996. On one hand there was a trend of decrease in stages-1 and -2 CRC ($P < 0.01$) and increase in stage-3 CRC ($P < 0.01$), but this was accompanied by a trend of decrease in stage-4 CRC ($P < 0.01$) at time of diagnosis (Table 2).

Jewish immigration

We examined the contribution of Jews immigrating to Israel since 1990 from the former Soviet Union (FSU) to the incidence rates, and calculated this rate for the peak immigration period 1996–2000. The CRC rates in both males and females were higher than those of the European–American born Jews but long-term residents in Israel. In 1996 the rate in new immigrants exceeded 55 out of 100,000 in men and 43 out of 100,000 in women. During the following period 1996–2000, the rate in the newcomers dropped 10% to 50 out of 100,000 in males and 39 out of 100,000 in females. Considering the latency period of CRC this trend can be explained by both a health-immigration effect and a better accessibility to health-care system in Israel than in their native land. However, in the year 2000, the higher rate differences between the new immigrants from the FSU and the entire population originating from Europe–America and immigrated to Israel in past years was still 4 out of 100,000 for males and 2 out of 100,000 for females [11].

Survival analysis

Overall CRC survival

Calculations were made separately for those who were diagnosed in the periods 1970–1978, 1979–1987 and 1988–1996 with a follow-up until the end of year 2000. The overall 5-year survival rate increased by 9%, from 36% at the first period to 40.8% in the second and reached 45.1% at the last period ($P < 0.01$). Females survived slightly better than males in all cancer stages and the gender gap in survival was 5.3% in the first period, 2.4% and 2.2% in the other two (Figures 5a and b) (Table 3).

Survival by CRC stage

Improvement in the survival rates was noted in all stages but least in stage 4, and in both sexes, during the three examined periods (Table 3) ($P < 0.01$ for each stage and

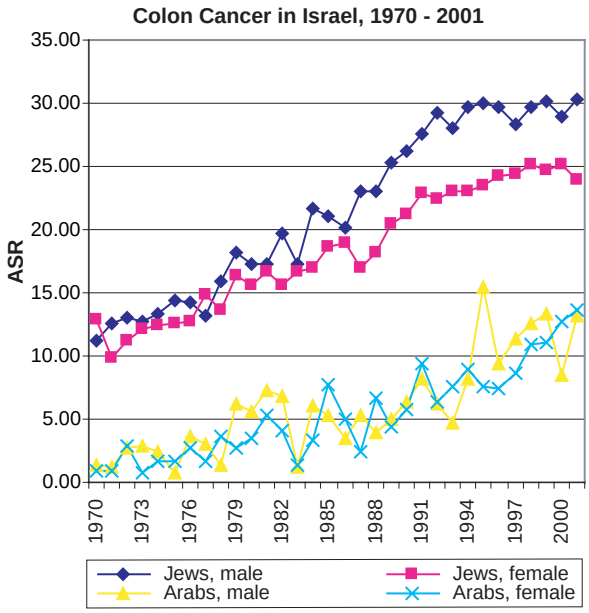


Figure 1. Incidence rates of colon cancers in Israel, by sex from 1970 to 2001. Note the increased incidence that occurred in Jews 1970–1992, especially in males ($P < 0.01$), and the plateau since then. In the Arab population, there was a gradual rise in incidence since 1980 and a more abrupt increase in the last decade.

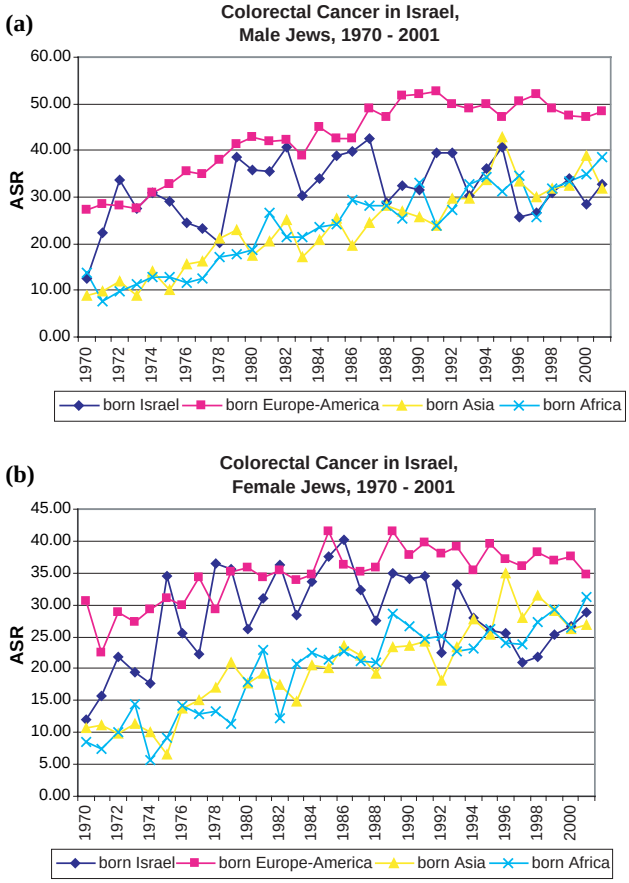


Figure 2. Incidence rates in Jews of colorectal cancers, by sex and continent of birth from 1970–2001. (a) Note the higher incidence in males born in Europe–America and the plateau since 1990. The incidence in Israeli born has decreased, the African–Asian born increased and the levels merged and plateau at a significantly lower level than the European–American ($P < 0.01$). (b) The trends in females were as above ($P = 0.03$).

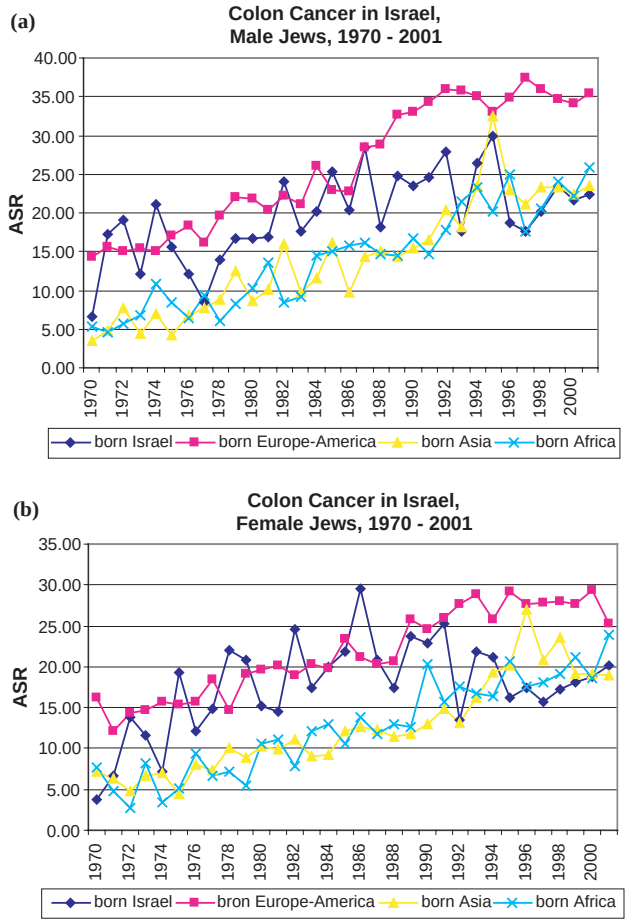


Figure 3. Incidence rates in Jews of colon cancer, by sex and continent of birth from 1970 to 2001. (a) Note the significantly higher incidence ($P < 0.01$) in men born in Europe–America and the lower, but uniform incidences of the other ethnic groups in the last five years. (b) Note the significantly higher incidence in females born in Europe–America and the lower, but uniform incidences of the other ethnic groups in the last five years.

Table 1. Colorectal cancer in Israel 1970–1996, incidence by origin and cancer stage.

Origin/ stage	All cases		Europen–American born		Asian–African born		Israeli born	
	Total	%	Total	%	Total	%	Total	%
All	38493		27917	72.5	6921	18.0	3655	9.5
Stages 0–1	9299	24.2	6995	75.2	1493	16.1	811	8.7
Stage 2	2482	6.5	1804	72.7	442	17.8	236	9.5
Stage 3	12276	31.9	8623	70.2	2439	19.9	1214	9.5
Stage 4	5214	13.6	3818	73.2	897	17.2	499	9.6

There were no differences in the proportions of ethnic groups at each colorectal stage.

for both sexes, other than stage 3 in men, $P = 0.03$). The most marked difference between sexes were in stages 1 and 2 and less in stage 3 – an average difference of 6.5% in the survival of those diagnosed at stage 1 in favor of women and 5.1% for those diagnosed in stage 2. The female to male survival rate ratio by stage shows no particular trend during the various time periods and it seems they were distributed randomly.

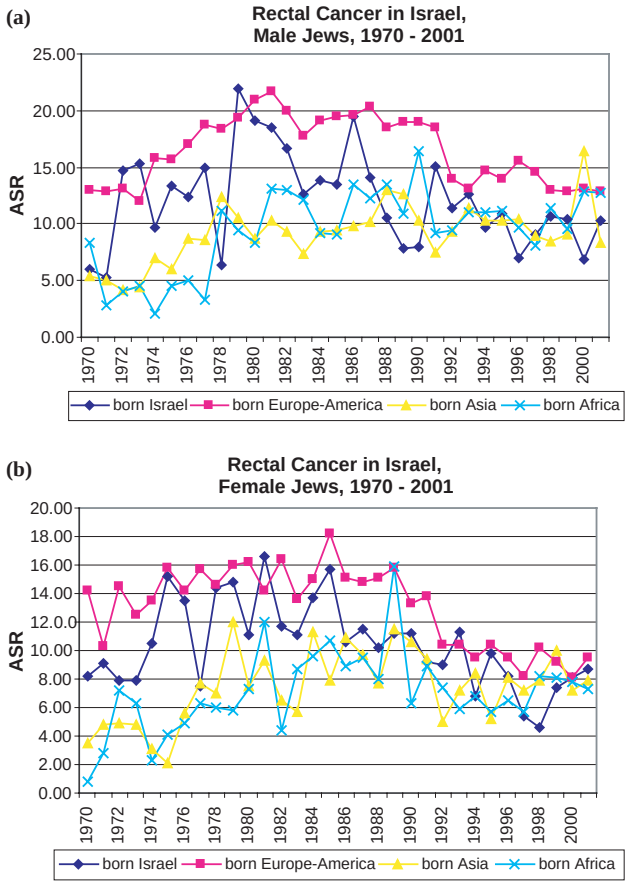


Figure 4. Incidence rates of Jews with rectal cancers, by sex and continent of birth from 1970–2001. (a) Note the initial rise in incidence ($P < 0.01$) in men of all ethnic groups from 1970 and since 1985, there was a decline and plateau since then. (b) Rectal cancer in Jewish females, 1970–2001. Note the initial rise in incidence in women of all ethnic groups from 1970 and since 1985, there was a decline and plateau since then.

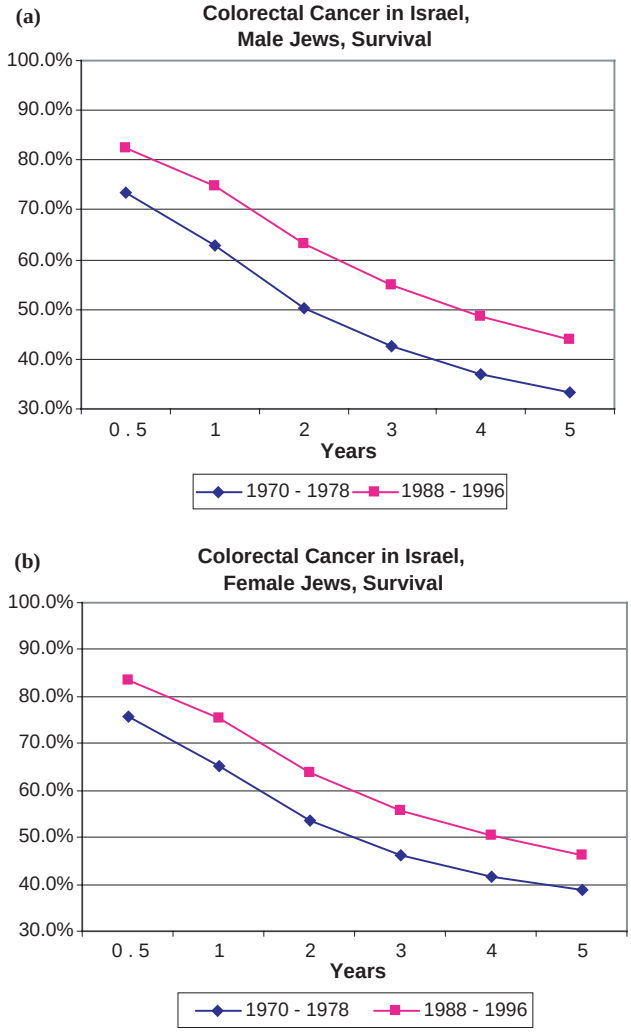


Figure 5. Five-year survival rates in Jews with colorectal cancer, by sex comparing 1970–1978 to 1988–1996. The mean survival improved by 9% [(a) men; (b) women], and was highest in women.

Table 2. Colorectal cancer in Israel, incidence by periods 1970–1996, cancer stage and sex.

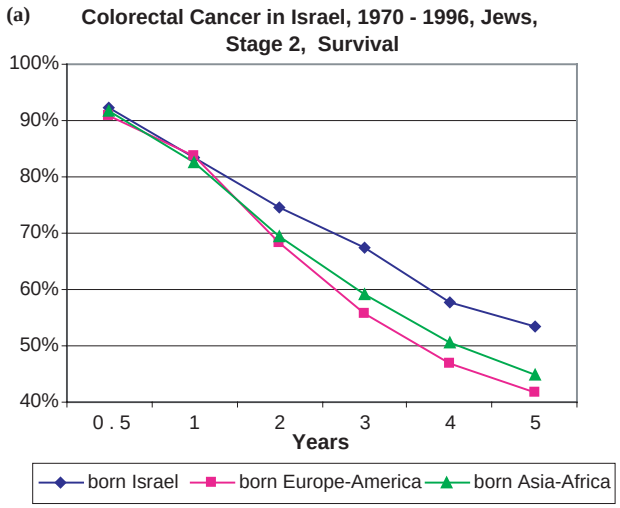
Period/stage	1970–1978		1979–1987		1988–1996	
	Total	%	Total	%	Total	%
Male Jews						
All	3558	33.4	6563	39.3	9442	43.9
Stages 0–1	1039	29.2	1601	24.4	2122	22.5
Stage 2	345	9.7	438	6.7	478	5.1
Stage 3	610	17.2	2113	32.2	3513	37.2
Stage 4	562	15.8	1075	16.4	1030	10.9
Female Jews						
All	3423	38.7	5885	42.0	8748	46.3
Stages 0–1	1011	29.5	1467	24.9	1879	21.5
Stage 2	324	9.5	404	6.9	438	5.0
Stage 3	569	16.6	1875	31.9	3301	37.2
Stage 4	542	15.8	961	16.3	929	10.6

The proportions of colorectal cancer in each stage changed significantly ($P < 0.01$) from 1970–1978 to 1988–1996.

Survival by CRC stage and ethnicity

Differences in survival by stage at time of diagnosis and ethnicity were examined in the Jewish population. For the entire period examined (1970–1996) the overall 5-year survival rate for Jews was 42.1%. Patients born in Europe–America had a survival rate of 41%, the Asia and Africa group had a 43% survival rate, while the Israeli born survived significantly better with an overall survival rate of 48.2% (Table 4). It should be noted that even the smallest group contained over 3000 persons. For the period 1988–1996, the 5-year survival rates improved. For European–American born, they were 43.1%, Asian 46.7%, African 47.5% and Israeli born 55.8%.

Ethnic differences in survival were more marked for stage 2 CRC overall 5-year survival for 1970–1996. The overall survival rate for Jews was 43.4%; lower for European–American born, better in Asian and African born and best in Israeli born ($P < 0.01$) (Figure 6a) (Table 4). Similarly, stage-3 CRC survival was lowest for European–American born, better in Asian and African born and best in Israeli born ($P < 0.01$) (Figure 6b) (Table 4).



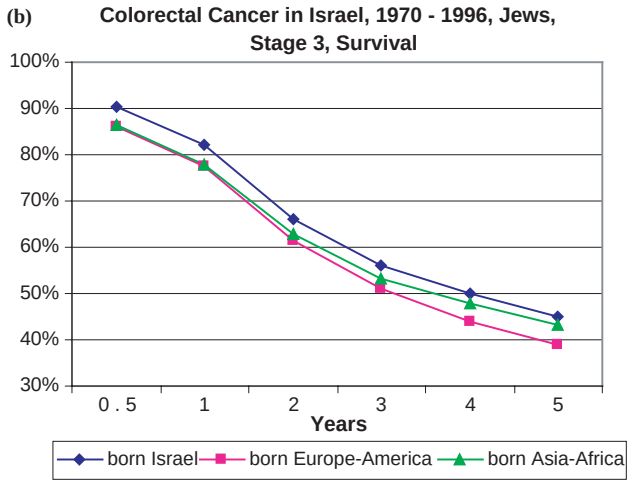
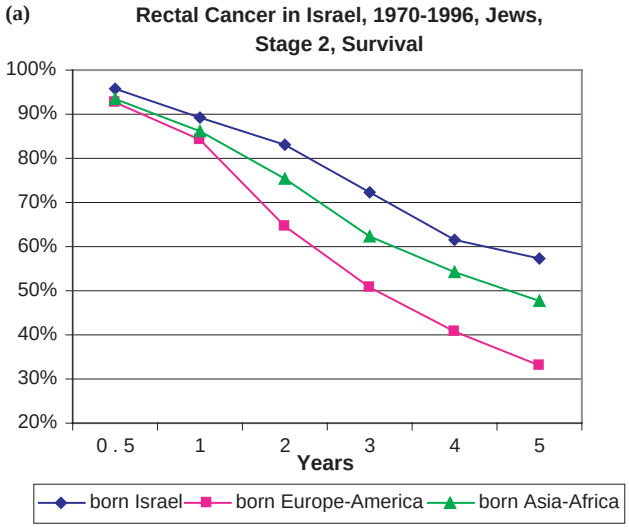


Figure 6. Survival from colorectal cancer, by continent of origin. Israeli born had a significantly better five-year survival for stages 2 and 3 colorectal cancer than European–American born ($P < 0.01$). (a) Men. (b) Women.



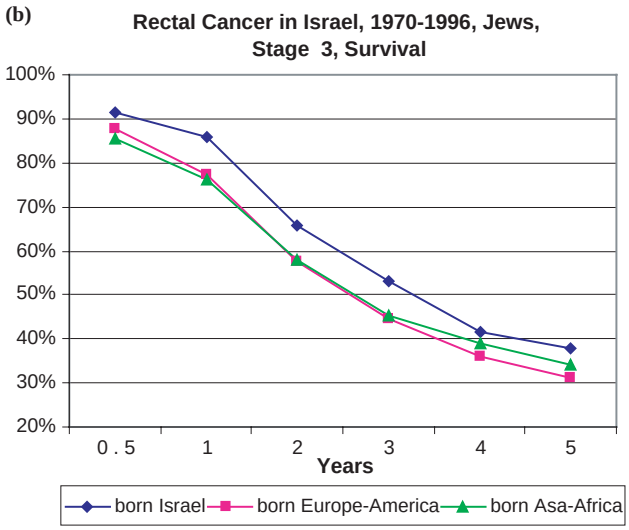


Figure 7. Survival from rectal cancer, by continent of origin. Israeli born had a significantly better five-year survival for stages 2 and 3 rectal cancer than European–American born. (a) Men ($P < 0.01$). (b) Women ($P = 0.02$).

Table 3. Colorectal cancer in Israel, survival by periods 1970–1996, cancer stage and sex.

Period/stage	1970–1978		1979–1987		1988–1996	
	Total	%, Alive	Total	%, Alive	Total	%, Alive
Male Jews						
All	3558	33.4	6563	39.8	9442	43.9
Stages 0–1	1039	57.3	1601	65.6	2122	67.2
Stage 2	345	33.3	438	42.0	478	45.4
Stage 3	610	24.8	2113	38.1	3513	42.6
Stage 4	562	3.4	1075	4.4	1030	4.7
Female Jews						
All	3423	38.7	5885	42.0	8748	46.3
Stages 0–1	1011	67.1	1467	70.5	1879	72.1
Stage 2	324	36.1	404	49.0	438	50.9
Stage 3	569	28.3	1875	38.2	3301	45.5
Stage 4	542	2.8	961	4.6	929	5.7

Comparing the period 1970–1978 to 1988–1996, survival improved, in women more than in men, for all cancer stages for both sexes ($P < 0.01$), other than stage 4 in men ($P = 0.03$).

Survival for rectal cancer

The overall 5-year survival for stage-2 rectal cancer was significantly better for Asian–African Jews as compared to European–American born, $P < 0.01$ (Figure 7a), while for stage 3, the differences were less $P = 0.02$ (Figure 7b).

Discussion

This long-term national analysis of Israeli-Jewish colorectal cancer incidence and mortality, confirms that Jewish immigrants, especially males, from Europe or Americas are at high risk for colon cancer and have the worst survival as compared to other immigrant populations. Conversely, the Israeli born has the lowest incidence and best survival. This is not due to differences in staging at diagnosis, or availability of

Table 4. Colorectal cancer in Israel 1970–1996, five-year survival by origin and cancer stage.

Origin/stage	All cases		European–American born		Asian–African born		Israeli born	
	Total	%, Alive	Total	%, Alive	Total	%, Alive	Total	%, Alive
All	38493	42.1	27917	41.0	6921	43.0	3655	48.2
Stages 0–1	9299	67.4	6995	66.0	1493	70.5	811	73.7
Stage 2	2482	43.4	1804	41.7	442	44.8	236	53.4
Stage 3	12276	40.4	8623	39.0	2439	43.3	1214	45.1
Stage 4	5214	4.5	3818	4.3	897	4.3	499	6.2

Israel-born had significantly better overall colorectal cancer survival compared to European–American born ($P < 0.01$). This was also true for stages 2 and 3 ($P < 0.01$).

cancer therapy. This higher risk of European born was illustrated by the highest colorectal cancer incidence that was identified in recent Jewish immigrants from the former Soviet Union. They are usually classified as 'Ashkenazi' Jews and they are at a higher than expected risk (compared to long-term immigrants to Israel of similar origin) and this can only be explained by exposure to differing lifestyles and diet. The markedly rising CRC incidence in Jews born in Asia and Africa is consistent with the effects of long-term diet and lifestyle, namely the 'westernization' of Mediterranean and Middle-Eastern people. As found in other immigrant populations, the change was most marked in the colon while rectal cancer has decreased and reached a plateau [1].

The limitations of this study include the Jewish ethnic classification. The 'European–American' geographic grouping also includes Jews who would be considered by themselves as non-Ashkenazim, usually 'Sephardim' – descendents of Jews expelled from Spain and Portugal [10]. Similarly, we do not know how Israeli-born Jews would be classified ethnically, Ashkenazi, Sephardi, or usually mixed. In addition, with the introduction of colonoscopic therapies, namely ambulatory polypectomy and mucosectomy, there is likely to have been a reduction in registration of 'early' cancer. This might explain the decrease in colorectal cancer stages 0–1 noted in the last decade of registration and for these reasons, we have not placed emphasis on analyzing this group. A further limitation is the lack of information on family history. We do know from a previous study, that familial CRC was more commonly found in the non-Ashkenazi CRC patients [4]. So, this cannot explain the higher risk for CRC in the European–American-born Jews.

Israeli born colorectal cancer patients had the lowest incidence and best survival of all populations. Israeli born Jews are the descendents of inter-ethnic marriages. From the Israeli demographic statistics, male immigrants to Israel married 22 to 40% outside their ethnic (continent of birth) group, while 60% of Israel-born men married non-Israeli born women [9].

Overall survival has significantly improved in the last decade. This was due to a decrease in stage-4 and increase in stage-3 cancers at the time of diagnosis of all ethnic groups. This is in contrast to the published findings of a similar sample of Israeli cancer patients [12].

Oncological therapy, surgical and medical, are uniformly available to all Israeli residents as all were insured voluntarily, and now compulsory, in one of four public medical insurances. The lack of therapy or deficient therapy cannot explain why survival is lowest in European born and best in Israeli born Jews. This was true for stage-2 cancer, which is rarely treated by chemotherapy, and stage-3 cancer that is almost always treated by post-surgery chemotherapy. Interestingly, rectal cancer which, in addition, is almost always treated with radiation, had the worst prognosis, stage for stage, in European born as compared to Asian and African born, while Israeli born had the best survival. These findings are not consistent with a very small published sample [13].

The reasons for this ethnic disadvantage, i.e., higher risk and worse prognosis of European born Jews are speculative. They include the occurrence of low penetrance susceptibility mutations, uncommon and unrecognized dominant mutations and especially diet and lifestyle [4, 5, 14–17]. The converse findings in Israeli born are, again, speculative. These include the suppression of low-penetrance genetic susceptibility by inter-ethnic marriages, adaptation to a more Mediterranean and less European diet and, possibly, better overall health.

In conclusion, Jews of European–American origins are at high risk for colon cancer and have the worst prognosis compared to other Jewish ethnic groups. The explanations are speculative, but include genetic susceptibility and deleterious diet and lifestyle.

Acknowledgements

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