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Liver and gallbladder cancer in immigrants to Sweden

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ABSTRACT

Background: The changes of cancer incidence upon immigration can be used as an estimator of environmental influence on cancer risk. We studied site-specific liver and biliary cancers in first-generation immigrants to Sweden with an aim to search for aetiological clues and to find evidence for indigenous incidence rates.

Material and methods: We used the nation-wide Swedish Family-Cancer Database to calculate standardised incidence ratios (SIRs) in immigrants compared to native Swedes.

Results: A total of 1428 cancers were identified in immigrants whose median ages (years) at immigration were 27 for men and 26 for women and whose median diagnostic ages were 64 and 66, respectively. The highest SIRs of 6.7 for primary liver cancer were observed for men from East Asia and sub-Saharan Africa. Increased SIRs were recorded for male immigrants from previous Yugoslavia (1.78), Southern Europe (2.91), Turkey (2.15) and Asian Arab countries (2.89). For gallbladder cancer, only women from the Indian subcontinent (3.84) and Chile (2.34) had increased risk while some Northern European immigrants showed decreased risks.

Conclusions: Primary liver cancer was increased in immigrants from endemic regions of hepatitis B virus infection but also from large regions lacking cancer incidence data, North Africa, Asian Arab countries, Turkey and previous Yugoslavia; these are probably intermediary risk regions for this infection. The consideration of these regions as risk areas would justify active diagnostic and vaccination programs. The increase in gallbladder cancer in Chileans and Indians suggests that some persistent damage was inflicted before emigration, characterisation of which will be a challenge for aetiological studies.

1. Introduction

According to the International Classification of Diseases revision 7 (ICD-7) primary liver and biliary tract tumours are classified as liver (ICD-7 code 155.0), gallbladder (155.1), extrahepatic bile ducts (155.2) and ampulla of Vater (155.3). The incidence of the two first ones is around 3/100,000 and the two latter ones below 1/100,000 in Sweden.[27] The incidence rates for liver cancer show very wide international variations depending on the distribution of the environmental risk factors: chronic infection by hepatitis B or C virus (HBV and HCV), cholangiogenic liver flukes, ingestion of aflatoxin

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B1 mycotoxin, alcohol-induced liver cirrhosis, metabolic syndrome (non-alcoholic fatty liver disease) and tobacco smoking.[4,15] In Europe there is about 20-fold difference in liver cancer incidence, increasing from the Netherlands and Belgium to Switzerland and Italy, Sweden being a low rate country.[6] Globally, Northern Europe and North America belong to low-risk areas while East and Southeast Asia and sub-Saharan Africa are the high-risk areas.[13] However, as reliable cancer registration is lacking in many parts of the world, the true incidence figures are not available. The International Agency for Research on Cancer has developed a system, GLOBOCAN, to estimate world cancer incidence, based on known and extrapolated rates.[13] Interestingly, for the present study, this system records most of previous Yugoslavia, Turkey, Iraq, Iran and most of North Africa as low-risk areas for liver cancer (not distinguishing subsites), while the only cancer registry reporting to quality controlled 'Cancer Incidence in Five Continents' is located in Algeria.[13] The international incidence rates for cancers in the biliary passages are not well known, with the exception of gallbladder cancer. The incidence variation in gall bladder cancer is smaller than that in liver cancer.[13] Risk factors of gallbladder cancer include gallstones, obesity and some structural abnormalities.[8] Cholangiocarcinoma in intrahepatic bile ducts may be caused by a persistent infection by liver flukes which are endemic in areas of Southeast Asia.[8] Other risk factors are primary sclerosing cholangitis and hepatolithiasis, but most patients in the developed countries have no obvious risk factors.[8]

We carried out a study on site-specific liver cancers in first-generation immigrants to Sweden with an aim to search for aetiological clues.[19,21] The median age at immigration has been in the 20s while liver cancers were diagnosed more than 20 years later. Thus before diagnosis, the immigrants have spent about one half of their life-time in Sweden with limited possibilities for exposure to the risk factors existing in their country of origin. A large difference in liver cancers rates in the immigrants compared to the Swedes would thus point to persistent effects carried along from the country of origin. Differences in incidence rates between immigrants and Swedes will also be informative of the international rate differences. The Swedish immigrant population constitutes some 15% of the country's population and it originates from practically all parts of the world.[9] Cancers were recorded by the nation-wide Cancer Registry. Liver cancer has not been considered in the previous Swedish immigrant studies because of small case numbers.[10,11] A general problem with liver cancer epidemiology may be the difficulties in distinguishing primary and metastatic liver cancers.

2. Subjects and methods

The study was based on the Swedish Family-Cancer Database with 11.8 million individuals of whom 15% were foreign born. Finns and Scandinavians were the largest immigrant groups but many other nationalities were included as discussed elsewhere.[9] The Swedish Family-Cancer Database was first

Table 1 – Case numbers and median immigration/diagnostic ages of primary liver and biliary cancers amongst first-generation immigrants to Sweden from 1958 to 2006.

Birth region	Number of cases		Age at immigration		Age of onset	
	Male	Female	Male	Female	Male	Female
Sweden	9893	11,515	–	–	70.0	70.0
Finland	163	281	24	23	66.0	65.0
Denmark	56	45	29	27	69.0	70.0
Norway	44	66	28	25	69.0	70.0
Baltic countries	38	39	26	27	69.0	72.0
Germany	64	68	27	26	66.5	69.0
Benelux	12	2	29	28	69.5	70.0
United Kingdom	6	7	29	28	55.0	59.5
Poland	19	28	30	28	62.5	62.0
Eastern Europe	40	22	28	28	64.5	65.5
Russia	10	17	29	31	69.5	71.5
Previous Yugoslavia	58	40	30	30	62.0	62.0
Greece	14	2	26	26	56.5	60.0
Southern Europe	38	7	27	27	62.0	65.0
Turkey	20	11	26	25	56.0	62.0
Iraq	3	1	31	30	54.0	63.0
Iran	6	4	28	29	64.0	60.5
Asian Arab Countries	15	8	28	26	58.0	63.5
Indian Subcontinent	2	6	25	20	46.5	45.5
Southeast Asia	10	11	26	28	54.5	52.0
East Asia	21	8	27	23	55.0	54.0
North America	15	14	28	28	73.0	72.0
Chile	10	10	29	29	55.0	54.0
Latin America	4	1	26	27	60.5	40.0
North Africa	12	0	27	27	55.5	–
Other Africa	27	11	28	26	53.0	58.0
Others	7	5	28	27	52.5	56.0
All immigrants	714	714	27	26	64.0	66.0

assembled from the national databases in 1996 and since then it has been periodically updated.[12] The Database contains nation-wide family data linked to the Swedish Cancer Registry, which was started in 1958. The Database contains those born in Sweden since 1932 with their biological parents and additionally data on immigrants were included. Immigrants were defined according to their birth country. First-generation immigrants were defined as those without identified parents in the Database. Follow-up was started on date of immigration or 1st January 1958, whichever came latest; if the date of immigration was missing, follow-up was started on the first year in which the immigrant was present at a census. Follow-up was terminated on diagnosis of cancer, death, emigration, last year presence at census or the closing date of our study, 31th December 2006. Standardised incidence ratios (SIRs) were calculated as the ratio of observed (*O*) to expected (*E*) number of cases. The expected numbers were calculated from 5 years age group, sex, period (10 years bands from 1958 to 2006) and tumour type-specific standard incidence rates. Cancer incidence for the native Swedish populations was used as reference. Confidence intervals (95% CI) were calculated assuming a Poisson distribution. SAS software ver. 9.1 was used for data analysis.

3. Results

The Family-Cancer Database registered 9893 male and 11,515 female liver cancers (including all subsites) in native Swedes and 714 male and 714 female cancers in first-generation immigrants (Table 1). The median age (years) at immigration was 27 for all men and 26 for all women; Finns had immigrated at the youngest age (24/23 years) and Iraqis and previous Yugoslavians at the oldest age (31/30 years). The median diagnostic ages were 64 for all immigrant men and 66 for all immigrant women. For primary liver cancer, the median diagnostic ages for immigrants were 63 for men and 65 for women; for gallbladder cancer these were 67 and 65, respectively (data not shown). For some immigrant groups, the diagnostic age was below 60 years which was largely explained by the recent entrance of these populations to Sweden.[9]

Primary liver cancer was diagnosed in 710 immigrants, male cases being twice as common as the female cases (Table 2). The highest SIRs were observed for men from East Asia (6.76) and other Africa (6.72, i.e., excluding North Africa which showed also an increased SIR of 3.72). Other male immigrants with increased SIR were from previous Yugoslavia (1.78), Southern Europe (2.91, i.e., Italy, France, Spain and Portugal), Turkey (2.15), Asian Arab countries (2.89) and Southeast Asia (4.39). Female SIRs were increased for Southeast Asia (3.12), East Asia (3.70) and other Africa (4.00); the female SIR for the Baltic countries was decreased (0.40).

The number of gallbladder tumours in immigrants was 407, four times more in women compared to men (Table 3).Only women from the Indian subcontinent (3.84) and men and women from Chile (2.34) had an increased risk;

Table 2 – SIRs for primary liver cancer amongst first-generation immigrants to Sweden.

Birth region	Male				Female				Both sexes			
	N	SIR	95% CI		*N*	SIR	95% CI		*N*	SIR	95% CI	
Sweden	5632	1.00			3239	1.00			8871	1.00		
Finland	105	1.15	0.94	1.39	69	0.82	0.64	1.04	174	0.99	0.85	1.15
Denmark	32	0.95	0.65	1.34	16	0.96	0.55	1.56	48	0.95	0.70	1.27
Norway	26	0.83	0.54	1.21	24	0.81	0.52	1.21	50	0.82	0.61	1.08
Baltic countries	17	0.80	0.47	1.28	5	**0.40**	0.13	0.93	22	**0.65**	0.41	0.99
Germany	40	1.15	0.82	1.56	28	1.15	0.76	1.66	68	1.15	0.89	1.45
Benelux	9	1.91	0.87	3.62	2	1.08	0.13	3.91	11	1.68	0.84	3.00
United Kingdom	6	1.27	0.47	2.77	2	0.87	0.11	3.15	8	1.14	0.49	2.25
Poland	12	1.00	0.52	1.75	13	1.38	0.74	2.36	25	1.17	0.76	1.72
Eastern Europe	24	1.21	0.78	1.80	13	1.43	0.76	2.44	37	1.28	0.90	1.76
Russia	7	0.90	0.36	1.85	2	0.40	0.05	1.43	9	0.70	0.32	1.33
Previous Yugoslavia	44	**1.78**	1.30	2.40	14	1.16	0.64	1.95	58	**1.58**	1.20	2.04
Greece	11	1.92	0.96	3.44	1	0.51	0.01	2.82	12	1.56	0.81	2.72
Southern Europe	29	**2.91**	1.95	4.18	2	0.61	0.07	2.21	31	**2.34**	1.59	3.33
Turkey	14	**2.15**	1.18	3.61	4	1.38	0.38	3.54	18	**1.92**	1.14	3.03
Iraq	2	0.47	0.06	1.70	1	0.62	0.02	3.48	3	0.51	0.11	1.50
Iran	5	0.86	0.28	2.00	0				5	0.60	0.19	1.39
Asian Arab Countries	12	**2.89**	1.49	5.05	3	1.75	0.36	5.11	15	**2.56**	1.43	4.22
Indian Subcontinent	2	0.83	0.10	2.99	2	1.91	0.23	6.92	4	1.16	0.32	2.96
Southeast Asia	9	**4.39**	2.01	8.33	6	**3.12**	1.14	6.79	15	**3.77**	2.11	6.22
East Asia	19	**6.76**	4.07	10.56	6	**3.70**	1.36	8.04	25	**5.64**	3.65	8.33
North America	5	0.43	0.14	1.00	2	0.28	0.03	1.03	7	**0.37**	0.15	0.77
Chile	7	1.99	0.80	4.11	3	1.49	0.31	4.35	10	1.81	0.87	3.33
Latin America	4	1.17	0.32	3.00	1	0.50	0.01	2.81	5	0.93	0.30	2.16
North Africa	10	**3.72**	1.78	6.83	0				10	**3.16**	1.52	5.81
Other Africa	25	**6.72**	4.35	9.92	6	**4.00**	1.47	8.70	31	**5.94**	4.03	8.43
Others	5	1.40	0.45	3.26	4	2.41	0.66	6.18	9	1.72	0.79	3.26
All immigrants	481	**1.34**	1.22	1.47	229	0.95	0.83	1.08	710	**1.19**	1.10	1.28

Bold type: 95% CI does not include 1.00.

Table 3 – SIRs for gallbladder cancer amongst first-generation immigrants to Sweden.

Birth region	Male				Female				Both sexes			
	N	SIR	95% CI		N	SIR	95% CI		N	SIR	95% CI	
Sweden	2146	1.00			5854	1.00			8000	1.00		
Finland	19	0.64	0.39	1.00	153	1.09	0.92	1.27	172	1.01	0.86	1.17
Denmark	6	0.52	0.19	1.13	17	**0.58**	0.34	0.93	23	**0.56**	0.36	0.84
Norway	7	0.62	0.25	1.28	28	**0.53**	0.35	0.76	35	**0.54**	0.38	0.75
Baltic countries	8	0.92	0.40	1.82	21	0.87	0.54	1.33	29	0.89	0.59	1.27
Germany	10	0.81	0.39	1.48	23	**0.53**	0.34	0.80	33	**0.59**	0.41	0.83
Benelux	1	0.64	0.02	3.58	0				1	0.21	0.01	1.20
United Kingdom	0				4	1.07	0.29	2.74	4	0.78	0.21	1.99
Poland	2	0.51	0.06	1.83	7	0.49	0.20	1.02	9	**0.50**	0.23	0.94
Eastern Europe	8	1.24	0.53	2.44	5	**0.34**	0.11	0.79	13	0.61	0.33	1.04
Russia	2	0.65	0.08	2.36	7	0.77	0.31	1.59	9	0.74	0.34	1.40
Previous Yugoslavia	4	0.59	0.16	1.50	15	0.90	0.50	1.48	19	0.81	0.49	1.26
Greece	0				0				0			
Southern Europe	3	0.93	0.19	2.73	4	0.73	0.20	1.87	7	0.80	0.32	1.66
Turkey	1	0.55	0.01	3.04	4	0.98	0.27	2.50	5	0.84	0.27	1.97
Iraq	0				0				0			
Iran	0				2	0.69	0.08	2.50	2	0.47	0.06	1.71
Asian Arab Countries	2	1.97	0.24	7.13	4	1.98	0.54	5.07	6	1.98	0.73	4.31
Indian Subcontinent	0				4	**3.84**	1.05	9.83	4	2.43	0.66	6.23
Southeast Asia	0				4	2.08	0.57	5.32	4	1.64	0.45	4.20
East Asia	1	1.23	0.03	6.86	2	1.03	0.12	3.73	3	1.09	0.22	3.19
North America	5	1.11	0.36	2.59	10	0.75	0.36	1.38	15	0.84	0.47	1.38
Chile	2	2.25	0.27	8.11	6	2.38	0.87	5.17	8	**2.34**	1.01	4.62
Latin America	0				0				0			
North Africa	1	1.43	0.04	7.98	0				1	0.83	0.02	4.61
Other Africa	0				4	2.58	0.70	6.60	4	1.64	0.45	4.20
Others	0				1	0.46	0.01	2.54	1	0.31	0.01	1.76
All immigrants	82	**0.70**	0.56	0.87	325	**0.81**	0.73	0.91	407	**0.79**	0.71	0.87

Bold type: 95% CI does not include 1.00.

Finnish men, Eastern European women and Danish, Norwegian, German and Polish female immigrants (and of both sexes) showed decreased risks.

Cholangiocarcinomas were analysed as a specific tumour type (Table 4), and Danish (2.34) and other African men (5.30) showed increased risks. Finnish women and all Finns had a decreased risk. We also analysed risks for cancers of the extrahepatic bile ducts (132 cases in immigrants) and of ampulla of Vater (99 cases). The cancers of extrahepatic bile ducts were increased in Baltic women (*N* = 11, SIR 2.18, 95% CIs 1.09–3.90); ampulla of Vater tumours were increased in Turkish women (*N* = 3, SIR 7.04, 95% CIs 1.45–20.57).

4. Discussion

Primary liver cancer was increased in many groups of first-generation immigrants, with highest risks for the East and Southeast Asian and African male and female immigrants. Chronic HBV infections are rare in Sweden and some 90% of the HBV-infected persons are immigrants from high-risk areas; HCV infections are however more common in Sweden and the patients are mainly natives many of whom are intravenous drug users.[17,24,26] Liver cancer develops typically two or more decades after viral infection and the risk may be up to 100-fold for those infected at birth.[8,26] Thus the present results on immigrants are likely to depend on infections contracted in the country of origin a few decades before immigration to Sweden. Aflatoxin exposure may have contributed to the DNA damage. Liver cancer risks have also been reported in Asian immigrants to Australia and North America.[5,14,20,23] Increased liver cancer risks were noted for sub-Saharan immigrants to France but no increases were noted for North Africans.[2,3]

The risks of gallbladder cancer were increased in female immigrants from Chile and the Indian subcontinent. Chile is reported to have some of the world's highest incidence rates of gallbladder cancer, suggested to be related to factors such as poor living conditions and unavailability of medical care and cholecystectomy.[1,22] The Chilean population arrived in Sweden shortly after the Pinochet military coup in 1973 and the median time lapse between cancer diagnosis and immigration was some 25 years. Thus some persistent insults predisposing to gallbladder cancer appeared to have taken place while the population still lived in Chile. Genetic factors cannot be excluded but Latin America is not generally a high-risk region.[13,22] The data on Indian gallbladder cancer rates differ extensively by cancer registry; female Delhi rate is 3-fold higher than the Swedish one while two other Indian registries report rates 20-fold below the Delhi rate.[13] These data suggest that the Indian immigrants originate from high-risk areas. Liver fluke infections have been common in Southeast Asian

Table 4 – SIRs for cholangiocarcinoma amongst first-generation immigrants to Sweden.

Birth region	Male				Female				Both sexes			
	N	SIR	95% CI		N	SIR	95% CI		N	SIR	95% CI	
Sweden	764	1.00			809	1.00			1573	1.00		
Finland	11	0.79	0.40	1.42	12	**0.52**	0.27	0.92	23	**0.63**	0.40	0.94
Denmark	11	**2.34**	1.17	4.18	3	0.69	0.14	2.02	14	1.55	0.85	2.60
Norway	3	0.70	0.14	2.04	4	0.54	0.15	1.38	7	0.60	0.24	1.23
Baltic countries	3	1.11	0.23	3.26	1	0.33	0.01	1.86	4	0.70	0.19	1.80
Germany	4	0.81	0.22	2.07	9	1.41	0.65	2.68	13	1.15	0.61	1.96
Benelux	3	4.33	0.89	12.66	0				3	2.53	0.52	7.40
United Kingdom	0				0				0			
Poland	2	1.15	0.14	4.15	2	0.74	0.09	2.69	4	0.90	0.25	2.31
Eastern Europe	4	1.36	0.37	3.49	1	0.40	0.01	2.23	5	0.92	0.30	2.15
Russia	1	0.96	0.02	5.37	2	1.54	0.19	5.58	3	1.29	0.27	3.76
Previous Yugoslavia	5	1.18	0.38	2.76	4	1.08	0.29	2.77	9	1.14	0.52	2.16
Greece	2	2.07	0.25	7.48	1	1.70	0.04	9.48	3	1.93	0.40	5.64
Southern Europe	1	0.65	0.02	3.65	0				1	0.42	0.01	2.32
Turkey	0				0				0			
Iraq	0				0				0			
Iran	1	0.84	0.02	4.68	0				1	0.50	0.01	2.77
Asian Arab Countries	3	3.75	0.77	10.96	0				3	2.25	0.46	6.59
Indian Subcontinent	1	2.33	0.06	13.00	0				1	1.43	0.04	7.97
Southeast Asia	2	5.38	0.65	19.45	0				2	2.07	0.25	7.48
East Asia	1	2.26	0.06	12.57	0				1	1.15	0.03	6.40
North America	1	0.63	0.02	3.51	0				1	0.30	0.01	1.67
Chile	1	1.54	0.04	8.56	1	1.56	0.04	8.71	2	1.55	0.19	5.60
Latin America	0				0				0			
North Africa	0				0				0			
Other Africa	4	**5.30**	1.44	13.57	1	2.26	0.06	12.58	5	**4.18**	1.36	9.74
Others	0				0				0			
All immigrants	64	1.18	0.91	1.50	41	**0.63**	0.45	0.86	105	0.88	0.72	1.07

Bold type: 95% CI does not include 1.00.

immigrants to United States of America but infections have been diagnosed even in migrants from South America and the former Soviet Union.[25] A quarter of the cases were diagnosed after 5 years of residence in the country. The increased risk of cholangiocarcinoma in Danish men is unlikely to be related to liver flukes while for African men the infection is possible as fluke infections are known in Africa.[18] A caveat for all the presented results is that a large number of comparisons were done and some findings may be due to chance.

The results allow the possibility to probe international differences in cancer incidence, extending to the populations lacking reliable cancer registration. As a note of caution, relating to the above-mentioned Indian discussion on gallbladder rates, the immigrants may be a highly selected group (such as opponents of suppressive regimes) with a cancer incidence deviating from the 'national' rate. Secondly, the emigration took place some decades ago after which the indigenous rates could have changed. Immigrants to Sweden have usually assimilated well into the society whereby many habits have been adjusted to the local conditions.[9] The availability of foreign food items has been limited and ethnic food shops have emerged relatively recently. The highest incidence of liver cancer in Europe has been in Southern Europe and the immigrants from this area had the highest liver cancer rate amongst European immigrants. According to the cancer statistics, Sweden and Finland have equal female incidence of gallbladder cancer while Norway and Denmark show only a half of the rates.[13] The SIRs were 1.01 for the Finnish, 0.56 for the Danish and 0.54 for the Norwegian immigrants, exactly in line with the rates in the countries of origin. Additionally, the above-mentioned example on the high risk of gallbladder cancer in Chilean immigrants attests to the predictivity of the immigrant rates for indigenous cancer rates. It is thus fair to assume that Turkey (low-risk according to GLOBOCAN), Asian Arab countries (low-risk according to GLOBOCAN; Saudi Arabia has an intermediary risk but very few immigrants in Sweden) and North African countries (low-risk according to GLOBOCAN for the main immigrant countries of Morocco, Algeria and Tunisia) belong to the intermediated-high-risk countries of primary liver cancer according to the present data in variance with GLOBOCAN 2002. Men from these areas have up to 2-fold risk of lung cancer compared to the Swedes (unpublished data) but the contribution of smoking to the observed excess is probably small because of the much stronger effect of smoking on lung (20-fold) than on liver (1.5-fold) cancer;[3] accordingly, Danish men and women have amongst the highest lung cancer rates the immigrants but no elevation of liver cancer risk. Female immigrants from these regions were not at an increased risk which is also in line with lower indigenous rates of liver cancer compared to East Asian and sub-Saharan high-risk areas. Even in the high-risk areas and Southern Europe, female rates of primary liver cancer are about one half of the male rates. One can question whether the immigrant populations may

have some habits that could increase their cancer risks in Sweden. Intravenous drug use is the most common risk factor for HCV infection but the proportion of immigrants amongst the HCV patients is less than their share in the Swedish population.[7] Infections by HBV have been reported in immigrants while visiting their high-risk countries of origin.[16]

In conclusion, primary liver cancer was increased in immigrants from endemic regions of HBV infection but also from North Africa, Asian Arab countries, Turkey and previous Yugoslavia which are probably intermediary risk regions for HBV infection. The consideration of these regions as risk areas would justify active diagnostic and vaccination programs amongst immigrants. The increase in gallbladder cancer in Chileans and in immigrants from the Indian subcontinent suggest that some persistent damage was inflicted before emigration, the causes of which will be a challenge for aetiological studies.

Conflict of interest statement

None declared.

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