Histology-specific risks in testicular cancer in immigrants to Sweden

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Abstract

The changes of cancer incidence upon immigration have been used as an estimator of environmental influence on cancer risk. The previous immigrant studies have indicated that the origins of testicular cancer are at an early age in life, probably in the intrauterine period. We wanted to reexamine the critical periods on histology-specific testicular cancer in sons of immigrants to Sweden. We used the nationwide Swedish Family-Cancer Database to calculate standardized incidence ratios (SIRs) for testicular cancer in sons of parents immigrating to Sweden from low- and high-risk countries compared with the native Swedes. Among the large immigrant groups, the SIRs for sons of two Finnish and Asian parents were decreased if the sons were born outside Sweden. The sons of a Danish immigrant couple showed an increased risk of testicular cancer. The changes in SIR were most systematic for seminoma. The present patterns of testicular cancer risk among sons of immigrants point to the early environmental risk factors, which influence the risk probably after the intrauterine period. These factors appear to influence seminoma risk in a more enduring way than they influence non-seminoma.

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Introduction

Testicular cancer is the most frequently occurring cancer in young white men aged 15–35 years. The incidence of testicular cancer has increased in many countries, including Sweden, for unknown reasons (Richiardi *et al.* 2004, Boyle & Levin 2008). Testicular cancers are predominantly germ cell tumors of two main types, seminomas and non-seminomas; the later include teratomas with somatic differentiation and undifferentiated embryonal tumors (Eble *et al.* 2003). However, about one half of germ cell tumors of the testis contain multiple histological types, and the remainder contains a single histological type (Eble *et al.* 2003). Similar incidence trends in seminoma and non-seminoma have been suggested to imply sharing of etiological factors between the histological types (Bray *et al.* 2006). The known risk factors of testicular cancer include undescended testis (cryptorchidism), testicular dysfunction, perinatal factors, prior history of cancer in

one testis (the opposite testis is at increased risk), and family history of testicular cancer, as reviewed (Eble *et al.* 2003, Boyle & Levin 2008). The first-generation immigrants to Sweden show generally a decreased risk of testicular cancer compared with the natives, but this difference tends to disappear in the next generation born in Sweden (Hemminki & Li 2002b, Hemminki *et al.* 2002). The effect was marked among the sons of the Finnish immigrants, whose risk was doubled compared with their fathers (Hemminki & Li 2002a, Ekblom *et al.* 2003, Montgomery *et al.* 2005). Among the sons of the Danish immigrants, coming from a high-risk country, an equally large but opposite change took place (Hemminki & Li 2002a). Low testicular cancer risks among immigrants were observed in Denmark, suggested to implicate the early life or the *in utero* period (Myrup *et al.* 2008).

Sweden is an excellent country to study cancer experience of the immigrants because of a uniform

cancer registration and health care system and the large number of immigrants from practically around the world: in the Family-Cancer Database with 11.8 million individuals, some 15% are foreign born (Hemminki et al. 2009). In the present paper, we examine risks of histology-specific testicular cancer in offspring immigrants to Sweden according to their and their parents' birth country in order to pinpoint the critical factors for the incidence change.

Subjects and methods

The Swedish Family-Cancer Database was first assembled from the national databases in 1996, and since then it has been periodically updated (Hemminki et al. 2001). The Database contains data on those born in Sweden since 1932 with their biological parents, and additionally data on immigrants are included. This Database is the largest in the world on familial cancer, and its updated version (2008, VIII) which has been supplied with longitudinal demographic and socio-economic data from each national census of 1960, 1970, 1980, 1990, and 2000 has been used for the present study (Hemminki et al. 2009).

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 the date of immigration or January 1, 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 the census, or the closing date of our study, December 31, 2006. Standardized incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year age group, sex, period (10-year bands from 1958 to 2006), and tumor 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.

Results

The Family-Cancer Database covered years 1958–2006 from the Swedish Cancer Registry, and it included 6833 testicular cancers in the native Swedish reference population. Table 1 shows the risk for testicular cancer in the first-generation immigrants.

Table 1 Median age at immigration and standardized incidence ratio (SIR) for testicular cancer by histological types among first-generation immigrants to Sweden 1958–2006

Birth region	Combined				Seminoma				Non-seminoma			
	N	SIR	95% CI	N	Age ^a	SIR	95% CI	N	Age	SIR	95% CI	
Sweden	6833	1.00		3720	–	1.00		3113	–	1.00		
Finland	66	0.45	0.35	38	25	0.45	0.32	28	22	0.46	0.31	0.67
Denmark	60	1.69	1.29	36	28	1.63	1.14	24	27	1.80	1.15	2.68
Norway	38	1.19	0.84	22	25	1.15	0.72	16	25	1.24	0.71	2.01
East Europe	44	0.77	0.56	28	25	0.77	0.51	16	27	0.76	0.44	1.24
Former Yugoslavia	39	0.56	0.40	16	30	0.38	0.21	23	25	0.85	0.54	1.28
Middle Europe	65	1.17	0.91	41	24	1.22	0.87	24	24	1.11	0.71	1.64
West and South Europe	23	0.64	0.40	15	25	0.71	0.40	8	29	0.53	0.23	1.05
Asia	48	0.29	0.21	24	29	0.25	0.16	24	24	0.34	0.22	0.51
Chile	35	2.21	1.54	20	30	2.12	1.29	15	23	2.34	1.31	3.86
North America	19	1.31	0.79	7	23	0.82	0.33	12	25	2.01	1.04	3.51
Other	26	0.29	0.19	18	27	0.36	0.21	8	26	0.21	0.09	0.41
All immigrants	463	0.65	0.59	265	24	0.62	0.55	198	23	0.68	0.59	0.78

^aMedian age at immigration. Bold denotes that the 95% CI does not include 1.00.

Table 2 Median age at immigration and standardized incidence ratio (SIR) for testicular cancer by histological types among sons of immigrants from low-risk regions

Birth region of parents	Birth region of sons	Combined			Seminoma			Non-seminoma							
		N	SIR	95% CI	N	Age ^a	SIR	95% CI	N	Age	SIR	95% CI			
Sweden Finland	Sweden	4709	1.00		2493	–	1.00		2216	–	1.00				
		48	0.77	0.57	25	–	0.89	0.58	1.31	23	–	0.68	0.43		
	Both parents	29	0.54	0.36	14	10	0.47	0.26	0.79	15	4	0.61	0.34		
		96	0.84	0.68	50	–	0.96	0.71	1.27	46	–	0.73	0.54		
	Father	29	0.52	0.35	14	10	0.46	0.25	0.78	15	4	0.60	0.33		
		150	0.90	0.76	79	–	1.00	0.79	1.24	71	–	0.81	0.64		
	Mother	30	0.54	0.36	14	8	0.46	0.25	0.77	16	4	0.63	0.36		
		17	1.49	0.87	2.38	7	–	1.65	0.66	3.40	10	–	1.39	0.67	
Former Yugoslavia	Sweden	17	1.03	0.60	1.66	6	14	0.85	0.31	1.85	11	12	1.17	0.59	2.10
		28	1.37	0.91	1.98	10	–	1.27	0.61	2.34	18	–	1.43	0.85	2.26
	Both parents	19	1.07	0.64	1.67	7	14	0.92	0.37	1.89	12	14	1.19	0.61	2.07
		20	1.25	0.77	1.94	9	–	1.51	0.69	2.87	11	–	1.10	0.55	1.97
	Father	19	1.07	0.64	1.67	7	17	0.92	0.37	1.89	12	12	1.19	0.61	2.07
		12	1.70	0.88	2.98	2	–	1.07	0.13	3.88	10	–	1.93	0.93	3.55
	Mother	13	0.46	0.25	0.79	6	13	0.57	0.21	1.23	7	11	0.40	0.16	0.82
		22	1.53	0.96	2.32	5	–	1.11	0.36	2.59	17	–	1.72	1.00	2.76
Asia	Sweden	16	0.51	0.29	0.84	6	13	0.51	0.19	1.11	10	11	0.52	0.25	0.95
		21	1.79	1.11	2.73	3	–	0.87	0.18	2.53	18	–	2.17	1.29	3.43
	Both parents	16	0.51	0.29	0.83	6	13	0.51	0.19	1.10	10	12	0.52	0.25	0.95

^aMedian age at immigration. Bold denotes that the 95% CI does not include 1.00.

Significantly decreased risks for all testicular cancer were observed for Finns (SIR 0.45), former Yugoslavians (0.56), Western and Southern Europeans (0.29), Asians (0.29), and others (0.29). Only Danish (1.69) and Chilean (2.21) immigrants showed increased risks. The observed overall changes were seen for both seminomas and non-seminomas, with the exception of former Yugoslavians with a risk for seminoma only and North Americans showing an increased risk of non-seminoma (2.01). For seminoma and non-seminoma, we show the median age at immigration which varied from 22 to 30 years.

The risks were analyzed for sons of the first-generation immigrants by considering the sons' and their parents' birth region. Table 2 covered three regions of low risk for the immigrant fathers of Table 1. Considering the combined histological types, the sons of two Finnish immigrants had an SIR of 0.77 (95% CIs 0.57–1.02) when they were born in Sweden compared with an SIR of 0.54 when they were born in Finland. The results were essentially identical for the combined histologies and seminoma, even if only the father or the mother was born in Finland. For seminoma, there was no risk if the sons were born in Sweden. For non-seminoma, all SIRs were of borderline significance, and the SIRs were only marginally higher if the birth county was Sweden instead of Finland. For the sons of the Yugoslavian immigrants, none of the SIRs were significant. For the sons of the Asian immigrants, the risks were decreased for the combined histologies and for non-seminomas when the sons were born in Asia, but they exceeded the Swedish rates when the sons were born in Sweden; notably the Sweden-born sons of the Asian mothers showed an increased risk of non-seminoma (2.17). Seminomas tended to be decreased for the sons of the Asia-born parents, but the case numbers were few in this relatively young immigrant population. The median ages at immigration, shown for seminoma and non-seminoma, were between 4 and 10 years for the sons of the Finnish immigrants, and between 11 and 17 years for the sons of Yugoslavian and Asian immigrants.

The risks for the sons of the Danish and Chilean immigrants are shown in Table 3. For the Danish immigrant sons, the risk for the combined histologies and for seminoma were increased but only if the sons were born in Denmark. No significant increases were observed for the Sweden-born sons of the Danish immigrants for the combined histologies or non-seminoma; however, all these SIRs were higher than the unity. No significant differences were observed for the sons of the Chilean immigrants.

Table 3 Median age at immigration and standardized incidence ratio (SIR) for testicular cancer by histological types among sons of immigrants from high-risk regions

Birth region of parents	Birth region of sons	Combined				Seminoma				Non-seminoma			
		N	SIR	95% CI	N	Age ^a	SIR	95% CI	N	Age	SIR	95% CI	N
Sweden	Both parents	4709	1.00		2493	–	1.00		2216	–	1.00		–
		13	1.77	0.94	7	–	1.85	0.74	6	–	1.68	0.62	3.67
		13	1.97	1.05	9	5	2.55	1.16	4	3	1.30	0.36	3.34
Denmark	Father	41	1.23	0.88	23	–	1.36	0.86	18	–	1.10	0.65	1.74
		17	2.19	1.28	10	5	2.41	1.16	7	3	1.94	0.78	4.00
		32	1.12	0.76	17	–	1.15	0.67	15	–	1.09	0.61	1.79
Chile	Mother	15	1.98	1.11	9	6	2.21	1.01	6	4	1.71	0.63	3.73
		1	1.35	0.03	0	–	–	–	1	–	1.79	0.05	9.97
		10	1.72	0.82	6	18	2.60	0.96	4	11	1.14	0.31	2.92
	Both parents	4	2.78	0.76	1	–	2.64	0.07	3	–	2.83	0.58	8.28
		10	1.71	0.82	6	18	2.59	0.95	4	11	1.13	0.31	2.90
		1	0.85	0.02	0	–	–	–	1	–	1.14	0.03	6.37
	Mother	10	1.70	0.81	6	19	2.57	0.94	4	12	1.13	0.31	2.88

^aMedian age at immigration. Bold denotes that the 95% CI does not include 1.00.

The median age at immigration of the sons of the Danish immigrants varied between 3 and 6 years, compared with 11 to 19 years for the sons of Chilean immigrants.

Discussion

Many immigrants have arrived as young couples (median age around 24 years) to Sweden, whereby their Sweden-born children have a completely indigenous genotype of their parental ethnicity (Hemminki *et al.* 2009). The results of the previous publications led us to conclude that the childhood environment, rather than genotype, is very important in setting the individual's cancer destiny (Hemminki & Li 2002b, Hemminki *et al.* 2002). Many immigrant groups originate from countries with no cancer registration, and, hence, the Swedish data may provide estimates on the indigenous cancer rates. Some surprising findings have been, for example, the testicular cancer rates in Chileans which are among the highest in the world. However, the overall testicular cancer rates recorded in the first-generation immigrants have agreed with pattern reported in the GLOBOCAN cancer maps (Ferlay *et al.* 2001, Boyle & Levin 2008), as also seen in Table 1. Caution is, however, warranted because the highest incidence of non-seminoma (25 years) coincides with the median immigration age of the first-generation immigrants; the peak incidence of seminoma is around 35 years (Hemminki & Li 2004). People with a diagnosed cancer are unlikely to emigrate to the same degree as their healthy country mates. For the children of immigrants who immigrated at a young age, the selection is not likely to be important; thus our main focus was on sons of the first-generation immigrants. Among second-generation seminoma patients, the highest median age at immigration, 18–19 years, was recorded for Chileans, while among non-seminoma patients, former Yugoslavians showed the highest median immigration age of 12–14 years.

The main conclusion of the present study was that among the large immigrant groups Finns, Asians, and Danes, the protection or risk observed in the first-generation remained in sons who were born in the region of origin, but the changes disappeared in sons born in Sweden. Whether only the mother or the father was the immigrant did not change the conclusion, but very few children in such mixed marriages were born outside Sweden. For Chileans, the number of affected sons was small to be conclusive. The sons of Yugoslavs did not show a clear risk pattern even though the case numbers were reasonable. The rates for the sons born

in the former Yugoslavia were higher than the Swedish rates, thus apparently higher than the rates in their immigrant fathers. The median time since immigration was 12 years, i.e. about 1994. Whether the local conflicts and refuge status influence the risks in the young sons remains a possible explanation. Overall, the present data do not point to *in utero* effects, because the *in utero* environment may be assumed to be largely similar whether the couples are having their children inside or outside Sweden, in the neighboring countries of Finland or Denmark. Rather, the early life environment of the sons predicates the risk. It is likely that the compatriot families keep some of their traditions in child raising, and these are not likely to change drastically upon immigration. Thus, the factors that tend to unify the testicular cancer rates of the immigrants with the Swedish level are probably among the assimilating guidelines and practices related to diet supplementation, nutrition, child care, and school start. However, the present case numbers are small and the importance of the early childhood and youth environment needs to be confirmed in other settings.

The question about histology remains somewhat unambiguous because of the small numbers in the younger immigrant populations of Yugoslavians, Asian, and Chileans. Among the sons of the Finns and Danes, born outside Sweden, the largest deviations from the Swedish histological patterns were observed for seminoma. This suggests that the origins of seminoma are more stably imprinted than those of non-seminoma, even though the peak incidence for seminoma is 10 years later than that of non-seminoma (Hemminki & Li 2004).

In summary, the present data on the patterns of testicular cancer risk among sons of immigrants appears to implicate the early environmental risk factors, which influence the risk probably after the intrauterine period. These factors appear to influence seminoma risk in a more enduring way than they influence non-seminoma.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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