Research Article

Cancer Epidemiology, Biomarkers & Prevention

Subtype-Specific Risk of Testicular Tumors among Immigrants and Their Descendants in Sweden, 1960 to 2007

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Abstract

Background: Testicular cancer is the most common cancer among young male adults in several populations. We compared subtype-specific risk of testicular cancer among migrants and their descendants to that of Swedish-born men to elucidate importance of genetic and environmental factors in testicular cancer etiology and the potential timing of exposures.

Methods: We followed a nationwide cohort of 3.6 million men ages 15 to 54 years between 1960 and 2007 through linkage between Swedish National Registers. Incidence rate ratio (IRR) adjusted for age and calendar year with 95% confidence intervals (CI) was estimated using Poisson regression.

Results: A total of 5,801 cases of testicular cancer occurred during 80 million person-years of follow-up. Compared with Swedish-born men, first-generation immigrants from low-risk countries had a lower risk (IRR, 0.43; 95% CI, 0.38-0.49) and first-generation immigrants from high-risk countries had a higher risk (IRR, 1.61; 95% CI, 1.42-1.83) of testicular cancer. The risk among first-generation immigrants varied remarkably by birthplace, reflecting the risk in their countries of birth. The risk of seminomas was statistically significantly modified by age at immigration and duration of residence among immigrants born in high-risk areas. We observed a statistically significantly convergence of risk among second-generation immigrants toward the risk in Sweden (IRR, 1.02; 95% CI, 0.93-1.12). The risk among second-generation immigrants was not affected by the duration of stay of their mothers in Sweden before pregnancy.

Conclusions: Our study provides evidence that life-style and environmental factors play an important role in the etiology of testicular cancer. *Cancer Epidemiol Biomarkers Prev; 19(4); 1053–65. ©2010 AACR.*

Introduction

Testicular cancer is the most common cancer among young male adults in most high-income countries with the majority of cases occurring between the ages 25 to 35 years (1, 2). The incidence of testicular cancer varies considerably worldwide, even between neighboring countries (1, 3). Among the Nordic countries, for instance, the rates vary 4-fold (4). Furthermore, an unexplained increase in testicular cancer occurrence in several populations has been observed over the past decades (5).

Apart from strong evidence in favor of a role for both inherited susceptibility and environmental factors, the etiology of testicular cancer largely remains unknown (6). It has been proposed that environmental factors cause testicular cancer by disrupting the hormonal regulation of the fetus (6), but studies of prenatal and perinatal factors in relation to risk have thus far been inconsistent.

Studies on migrants and their descendants may provide clues to the importance of environmental and genetic factors in the etiology of testicular cancer. In Sweden, the high proportion of foreign-born residents with a vast majority from other Nordic countries and a well-established system of population-based registers provide a unique opportunity to conduct migrant studies on testicular cancer. However, previous migrant studies in Sweden either did not focus on testicular cancer per se or have been small and lacked statistical power, which hindered any definitive conclusion (7-9).

In this nationwide cohort study, we compared the risk of testicular cancer and its histopathologic subtypes

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Table 1. IRR and 95% CI of testicular cancer among first- and second-generation immigrants ages 15 to 54 y old compared with Swedish-born men in Sweden by Birth Region/Country, 1960 to 2007

Immigrant/parental country of birth	First-generation immigrants				Second-generation immigrants*				$IRR_{country\ of\ birth}$†
	No. of men	Cases	PYRS‡	IRR§ (95% CI)	No. of men	Cases	PYRS‡	IRR§ (95% CI)	
Africa	49,386	9	529	0.16 (0.08-0.31)	8,538	5	75	0.77 (0.32-1.85)	0.06
Northern Africa	12,383	5	161	0.32 (0.13-0.76)	4,155	2	39	0.57 (0.14-2.26)	0.09
Other regions	37,003	4	368	0.10 (0.04-0.27)	4,401	3	36	1.01 (0.33-3.14)	0.1
Asia	188,450	58	2,003	0.28 (0.21-0.36)	28,836	21	218	1.21 (0.79-1.86)	0.09
Eastern Asia	14,069	5	119	0.42 (0.17-1.00)	2,096	4	26	1.80 (0.68-4.81)	0.07
Southern Asia	73,452	23	839	0.27 (0.18-0.40)	10,552	2	74	0.36 (0.09-1.45)	0.09
Iran	33,547	16	463	0.34 (0.21-0.55)	3,793	1	20	0.77 (0.11-5.47)	0.13
Other‖	39,905	7	376	0.18 (0.09-0.38)	6,809	1	54	0.24 (0.03-1.67)	0.09
Western Asia	100,929	30	1,045	0.27 (0.19-0.39)	16,438	15	119	1.55 (0.93-2.57)	0.22
Iraq	48,374	5	354	0.13 (0.05-0.31)	1,925	0	9	N/A	0.14
Lebanon	13,545	10	179	0.51 (0.27-0.95)	3,125	0	15	N/A	0.19
Syria	9,026	5	113	0.42 (0.18-1.01)	2,548	4	14	4.03 (1.51-10.75)	0.29
Turkey	21,764	9	330	0.27 (0.14-0.53)	9,034	10	76	1.54 (0.82-2.86)	0.2
Other‖	8,220	1	69	0.14 (0.02-1.02)	1,544	1	15	0.72 (0.10-5.10)	0.23
Europe	437,526	387	6,349	0.80 (0.72-0.89)	289,443	523	6,030	1.01 (0.93-1.11)	0.73
Eastern Europe	53,754	51	708	0.89 (0.67-1.17)	25,092	61	490	1.49 (1.16-1.92)	0.42
Ex-Czechoslovakia¶	4,525	7	81	1.20 (0.57-2.52)	3,350	10	71	1.62 (0.87-3.01)	0.98
Ex-Soviet Union¶	7,515	3	68	0.51 (0.16-1.57)	3,871	14	110	1.74 (1.03-2.94)	0.28
Hungary	8,606	14	185	1.14 (0.68-1.93)	6,155	16	126	1.33 (0.81-2.17)	0.95
Poland	23,285	20	266	0.85 (0.55-1.32)	10,638	21	168	1.56 (1.01-2.39)	0.66
Other‖	9,823	7	108	0.70 (0.33-1.47)	1,647	1	24	0.48 (0.07-3.41)	0.31
Northern Europe	233,473	200	3,530	0.79 (0.68-0.91)	264,330	470	5,593	0.99 (0.90-1.08)	1.04
Denmark	36,721	60	433	1.90 (1.47-2.45)	25,771	59	625	1.14 (0.88-1.47)	1.77
Estonia	3,648	4	78	0.94 (0.35-2.51)	7,645	16	237	0.84 (0.51-1.37)	0.34
Finland	134,114	80	2,432	0.48 (0.38-0.59)	111,449	181	2,264	0.88 (0.76-1.03)	0.51
Norway	32,384	37	342	1.39 (1.00-1.92)	30,976	68	835	1.08 (0.85-1.37)	1.85
United Kingdom	17,470	17	180	0.98 (0.61-1.58)	5,298	7	82	1.00 (0.48-2.11)	1.09
Other‖	9,136	2	65	0.33 (0.08-1.31)	2,344	4	53	0.94 (0.35-2.51)	0.48
Southern Europe	105,731	69	1,466	0.56 (0.44-0.70)	28,284	33	411	0.81 (0.57-1.14)	0.5
Bosnia	26,490	20	260	0.73 (0.47-1.14)	452	1	5	1.91 (0.27-13.58)	0.78
Ex-Yugoslavia¶	51,437	38	772	0.59 (0.43-0.82)	15,853	25	215	1.14 (0.77-1.70)	0.78
Greece	11,965	8	202	0.52 (0.26-1.04)	4,542	1	60	0.17 (0.02-1.18)	0.45
Other‖	15,839	3	231	0.17 (0.05-0.52)	7,883	6	136	0.46 (0.21-1.03)	0.44

(*Continued on the following page*)

Table 1. IRR and 95% CI of testicular cancer among first- and second-generation immigrants ages 15 to 54 y old compared with Swedish-born men in Sweden by Birth Region/Country, 1960 to 2007 (Cont'd)

Immigrant/parental country of birth	First-generation immigrants				Second-generation immigrants*				$IRR_{country\ of\ birth}$†
	No. of men	Cases	PYRS‡	IRR§ (95% CI)	No. of men	Cases	PYRS‡	IRR§ (95% CI)	
Western Europe	44,568	67	645	1.44 (1.14-1.84)	35,358	92	858	1.22 (0.99-1.50)	1.32
Austria	4,413	7	94	1.17 (0.56-2.45)	4,698	7	109	0.72 (0.34-1.50)	1.47
France	6,621	9	60	1.52 (0.79-2.92)	2,019	4	40	1.19 (0.45-3.18)	1.13
Germany	25,133	37	402	1.36 (0.99-1.89)	25,220	71	636	1.27 (1.01-1.61)	1.52
The Netherlands	4,882	7	51	1.65 (0.78-3.46)	2,325	8	51	1.78 (0.89-3.55)	0.99
Switzerland	2,368	7	27	3.37 (1.61-7.08)	1,150	1	27	0.44 (0.06-3.11)	1.76
Other‖	1,151	0	11	N/A	464	2	9	2.52 (0.63-10.07)	1.1
Latin America	37,374	58	471	1.26 (0.98-1.64)	8,293	4	67	0.75 (0.28-2.00)	0.39
Chile	15,794	46	236	2.01 (1.50-2.68)	4,017	2	24	1.19 (0.30-4.78)	1.25
Other‖	21,580	12	235	0.52 (0.30-0.92)	4,543	2	45	0.53 (0.13-2.10)	0.36
Northern America	15,451	16	149	1.17 (0.72-1.91)	8,897	23	229	1.49 (0.99-2.24)	0.94
United States	13,214	14	128	1.21 (0.72-2.04)	8,031	21	211	1.49 (0.97-2.29)	0.96
Other‖	2,237	2	21	0.95 (0.24-3.79)	875	2	18	1.40 (0.35-5.58)	0.78
Oceania	4,041	2	27	0.61 (0.15-2.43)	450	1	4	2.80 (0.39-19.89)	0.73

*Data on second-generation immigrants whose parents were born in different countries has been separately reported in both corresponding parental country of birth.

†ASRs in countries of birth, as reported in GLOBOCAN2002, relative to ASR in Sweden.

‡PYRS, person-years at risk divided by 1,000.

§IRRs are adjusted for attained age and calendar period of year. Swedish-born men with both parents born in Sweden were the reference group.

‖Countries with fewer than five cases of testicular cancer.

¶Ex-Czechoslovakia includes Czech Republic and Slovakia. Ex-Soviet Union includes Belarus, Moldova, Russian Federation, and Ukraine. Ex-Yugoslavia includes Croatia, Macedonia, Serbia, Slovenia, and Montenegro.

Table 2. IRR of testicular cancer among first- and second-generation immigrants ages 15 to 54 y in Sweden by immigrant/parental country of birth and histopathologic subtypes, 1960 to 2007

	Risk in country of birth*		All histopathologic subtypes			Nonseminomas			Seminomas		
	Immigrant	Parental	Cases	PYRS†	IRR‡ (95% CI)	Cases	PYRS†	IRR‡ (95% CI)	Cases	PYRSv	IRR‡ (95% CI)
Swedish born	—	—	4,733	64,152	1 (Reference)	2,235	64,097	1 (Reference)	2,449	64,119	1 (Reference)
First generation vs Swedish born	—	—	—	—	—	—	—	—	—	—	—
One/both parents Swedish born	—	—	18	253	0.91 (0.57-1.45)	10	253	1.02 (0.55-1.89)	8	253	0.83 (0.41-1.65)
No parents Swedish born	—	—	—	—	—	—	—	—	—	—	—
	High	—	250	2,086	1.61 (1.42-1.83)	102	2,084	1.58 (1.30-1.93)	145	2,085	1.62 (1.37-1.92)
	Low	—	262	7,190	0.43 (0.38-0.49)	130	7,188	0.50 (0.42-0.59)	126	7,188	0.37 (0.31-0.45)
Second generation vs Swedish born	—	—	—	—	—	—	—	—	—	—	—
Father foreign born	—	High	103	1,091	1.14 (0.93-1.38)	52	1,090	1.16 (0.88-1.53)	49	1,090	1.08 (0.81-1.44)
	—	Low	74	906	0.89 (0.71-1.12)	36	906	0.81 (0.58-1.12)	37	906	0.99 (0.71-1.37)
Mother foreign born	—	High	99	1,207	1.05 (0.86-1.28)	42	1,206	0.94 (0.69-1.28)	57	1,206	1.16 (0.90-1.51)
	—	Low	113	1,382	0.96 (0.80-1.16)	49	1,381	0.83 (0.62-1.10)	63	1,381	1.10 (0.86-1.41)
Both foreign born	—	High	63	470	1.55 (1.21-1.99)	26	470	1.30 (0.88-1.91)	36	470	1.77 (1.27-2.45)
	—	Low	86	1,109	0.85 (0.68-1.05)	49	1,108	0.88 (0.66-1.17)	36	1,108	0.80 (0.57-1.11)
At least one parent foreign born	—	High	265	2,768	1.18 (1.04-1.33)	120	2,766	1.10 (0.91-1.32)	142	2,766	1.24 (1.05-1.47)
	—	Low	273	3,397	0.90 (0.80-1.02)	134	3,395	0.84 (0.70-1.00)	136	3,396	0.97 (0.82-1.16)
Second generation vs first generation§	—	—	—	—	—	—	—	—	—	—	—
Father foreign born	—	High	103	1,091	0.72 (0.57-0.92)	52	1,090	0.72 (0.51-1.02)	49	1,090	0.70 (0.50-0.98)
	—	Low	74	906	2.11 (1.61-2.77)	36	906	1.65 (1.13-2.42)	37	906	2.92 (1.99-4.30)
Mother foreign born	—	High	99	1,207	0.66 (0.52-0.84)	42	1,206	0.58 (0.40-0.84)	57	1,206	0.73 (0.54-1.00)
	—	Low	113	1,382	2.20 (1.76-2.76)	49	1,381	1.67 (1.20-2.34)	63	1,382	2.99 (2.19-4.07)
Both foreign born	—	High	63	470	1.01 (0.76-1.34)	26	470	0.81 (0.52-1.28)	36	470	1.14 (0.78-1.66)
	—	Low	86	1,109	1.96 (1.51-2.54)	49	1,108	1.82 (1.29-2.58)	36	1,108	2.22 (1.50-3.29)
At least one parent foreign born	—	High	265	2,768	0.75 (0.63-0.90)	120	2,766	0.68 (0.52-0.89)	142	2,766	0.79 (0.62-1.01)
	—	Low	273	3,397	2.10 (1.76-2.51)	134	3,395	1.68 (1.31-2.17)	136	3,396	2.74 (2.12-3.53)

*Stratification for second-generation immigrants was based on the risk in parental country of birth (Table 1; derived from GLOBOCAN2002). We grouped second-generation immigrants as the low-risk group if both parents were from areas with an IRR of ≤0.8; otherwise, we grouped them as the high-risk group. For immigrants with one parent born outside Sweden, we grouped them as the low-risk group if parents born outside Sweden were from areas with an IRR of ≤0.8; otherwise, we grouped them as the high-risk group. We stratified first-generation immigrants based on the risk in country of birth. If immigrants were from areas with an RR of ≤0.8, we grouped them as the low-risk group; otherwise, we grouped them as the high-risk group.

†PYRS, person-years at risk divided by 1,000.

‡IRRs are adjusted for attained age and calendar period of year.

§IRRs are adjusted for attained age (15-24 y, 25-29 y, 30-34 y, 35-39 y, 40-44 y, and 45-54 y) and calendar period of year (1960-1969 y, 1970-1979 y, 1980-1989 y, 1990-1999 y, and 2000-2007 y).

among immigrants and their descendants to that of Swedish-born men. To clarify the timing of exposure influences on testicular cancer, we studied the risk among immigrants by their age at immigration and duration of residence, and among the immigrants' sons by the length of time that their mothers stayed in Sweden before pregnancy. Although epidemiologic data and histopathologic studies have implicated a prenatal etiology of testicular cancer (10), studies of the association between cryptorchidism and testicular cancer have indicated that part of the risk of developing testicular cancer is determined postnatal (11, 12). In the present study, we therefore aimed particularly to study the timing of immigration in relation to the risk of testicular cancer in greater detail than previous studies.

Materials and Methods

Database

We used the newly established Health and Migration Cohort-2007. This cohort was built by linkage between 14 Swedish national registers to study cancer, cardiovascular, and psychiatric diseases among immigrants and their descendants compared with Swedish-born residents. The linkage has been completed by 10-digit personal identity number that is maintained by the National Tax Board for all individuals that have resided in Sweden since 1947 (13). The data used in this study are part of the Health and Migration Cohort and includes the following: (*a*) The Cancer Register containing data on all cases of cancer since 1958. The completeness of cancer registration and the percentage of cytologically or histologically verified cases is considered to be close to 100% (14); (*b*) The Total Population Register at Statistics Sweden, which contains information on demographic variables and data on emigration and immigration for Sweden (15); (*c*) The Cause of Death Register, which contains information on the date of death and underlying cause of death since 1952 (16); and (*d*) The Multi-Generation Register that contains links between children and parents through their personal identity numbers for all Swedish inhabitants born after 1931 who were alive in 1960 (17).

The linkages have been completed by Statistics Sweden and the Centre for Epidemiology at the National Board of Health and Welfare. To ensure confidentiality, the personal identity numbers were replaced by serial numbers through Statistics Sweden. The study was approved by the Regional Board of The Ethical Committee, Stockholm.

Study cohort

The study cohort consisted of men ages 15 to 54 y with known individual and parental country of birth who were born after January 1, 1931 and who lived in Sweden at any time during January 1, 1960 and December 31, 2007. For persons born abroad, who had no registration of the parental country of birth, it was assumed that the parents originated from the same country as their child. The cohort consisted of three groups, men born outside of Sweden called the first-generation immigrants, men born in Sweden with at least one parent born outside of Sweden called the second-generation immigrants, and Swedish-born men with both parents born in Sweden called Swedish-born.

There were 3,722,551 men ages 15 to 54 years with known parental country of birth registered in the Swedish Total Population Register between 1960 and 2007. We excluded men who died (1,161 men), emigrated (122,001 men), or had a history of testicular cancer (28 men) before entry into the cohort, and immigrants for whom information about country of birth were missing (1,653 men) from the at-risk population. The final cohort included 3,597,708 men ages 15 to 54 y, of whom 732,228 were first-generation immigrants, 312,275 were second-generation immigrants, and 2,553,205 were Swedish-born men. All cohort members were either alive or free of testicular cancer at the start of follow-up.

Follow-up

The cohort members were followed from January 1, 1960, first immigration date for immigrants or date of birth, whichever occurred last, until they exited from the cohort, which was the date of diagnosis of cancer (ICD-7 code: 178 Malignant Neoplasm of Testis), first emigration date, death, or end of follow-up (December 31, 2007), whichever occurred first. We categorized testicular cancer into seminomas and nonseminomas (including embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac carcinoma) based on their histopathologic morphology.

Classification of the country of birth

We classified foreign-born individuals by their country of birth into six continents. We further subdivided continents into world regions, as defined by the United Nations Population Division. Due to lack of power, we report Africa and Oceania without their subdivided regions. We also pooled data for south-central and south-eastern Asia and report it as southern Asia. As for country level, we report only countries having five or more cases of testicular cancer. For detailed information about the final classification, please see Table 1.

Statistical methods

We calculated incidence rate ratios (IRR) with 95% confidence intervals (CI) using Poisson regression models. All analyses were adjusted for attained age (age at follow-up) and calendar period of follow-up in 2-y categories, unless otherwise stated. In addition, we performed the analysis among first-generation immigrants stratified by age at immigration (younger than 5 y, 5-14 y, 15-24y, and 25 y or older) and duration of residence in Sweden (shorter than 5 y, 5-9 y, 10-19 y, and 20 y or longer). To exclude plausible prevalent cases that occurred before immigration, we repeated the analysis after excluding cases within the first 2 y of immigration. The results were not statistically significantly different and, thus, not reported.

Table 3. IRR and 95% CI of testicular cancer among first-generation immigrants ages 15 to 54 y in Sweden compared with Swedish-born men by duration of residence, age at immigration and histopathologic subtypes, 1960 to 2007

		Immigrants from high-risk areas			Immigrants from low-risk areas		
		Cases	PYRS*	IRR† (95% CI)	Cases	PYRS*	IRR† (95% CI)
All	Age at immigration,‡ y						
	<5	30	160	2.28 (1.59-3.27)	32	582	0.61 (0.43-0.87)
	5-14	33	255	1.68 (1.20-2.37)	42	1,106	0.48 (0.35-0.65)
	15-24	74	673	1.47 (1.17-1.85)	86	2,375	0.41 (0.33-0.50)
	≥25	86	754	1.38 (1.12-1.71)	76	2,585	0.34 (0.27-0.42)
	Swedish-born	4,733	64,152	1 (Reference)	4,733	64,152	1 (Reference)
				$P_{homogeneity}$ = 0.14 P_{trend} = 0.02			$P_{homogeneity}$ = 0.03 P_{trend} = 0.01
	Duration of residence,‡ y						
	<5	69	478	1.54 (1.21-1.95)	55	1,708	0.35 (0.26-0.45)
	5-9	31	324	1.16 (0.81-1.65)	56	1,361	0.45 (0.34-0.58)
	10-19	61	549	1.54 (1.19-1.98)	72	2,084	0.41 (0.33-0.52)
	≥20	62	492	1.83 (1.43-2.36)	53	1,494	0.44 (0.34-0.58)
	Swedish born	4,733	64,152	1 (Reference)	4,733	64,152	1 (Reference)
				$P_{homogeneity}$ = 0.22 P_{trend} = 0.06			$P_{homogeneity}$ = 0.49 P_{trend} = 0.04
Nonseminomas	Age at immigration,‡ y						
	<5	11	160	1.64 (0.91-2.97)	21	582	0.74 (0.48-1.13)
	5-14	13	255	1.31 (0.76-2.27)	23	1,105	0.48 (0.32-0.72)
	15-24	28	672	1.24 (0.85-1.80)	43	2,375	0.43 (0.32-0.58)
	≥25	38	754	1.82 (1.32-2.52)	30	2,585	0.40 (0.28-0.57)
	Swedish born	2,235	64,097	1 (Reference)	2,235	64,097	1 (Reference)
				$P_{homogeneity}$ = 0.44 P_{trend} = 0.32			$P_{homogeneity}$ = 0.19 P_{trend} = 0.02
	Duration of residence,‡ year						
	<5	42	478	1.90 (1.40-2.57)	24	1,707	0.33 (0.20-0.44)
	5-9	12	324	1.06 (0.60-1.87)	32	1,361	0.57 (0.40-0.80)
	10-19	21	548	1.35 (0.88-2.08)	38	2,084	0.53 (0.38-0.73)
	≥20	15	492	1.35 (0.81-2.24)	23	1,494	0.55 (0.37-0.84)
	Swedish born	2,235	64,097	1 (Reference)	2,235	64,097	1 (Reference)
				$P_{homogeneity}$ = 0.24 P_{trend} = 0.12			$P_{homogeneity}$ = 0. 04 P_{trend} = 0.08

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Table 3. IRR and 95% CI of testicular cancer among first-generation immigrants ages 15 to 54 y in Sweden compared with Swedish-born men by duration of residence, age at immigration and histopathologic subtypes, 1960 to 2007 (Cont'd)

		Immigrants from high-risk areas			Immigrants from low-risk areas		
		Cases	PYRS*	IRR† (95% CI)	Cases	PYRS*	IRR† (95% CI)
Seminomas	Age at immigration,‡ year						
	<5	19	160	3.02 (1.92-4.74)	10	582	0.43 (0.23-0.81)
	5-14	19	255	2.00 (1.27-3.14)	18	1,105	0.46 (0.29-0.73)
	15-24	46	673	1.70 (1.27-2.27)	42	2,375	0.38 (0.28-0.52)
	≥25	46	754	1.13 (0.85-1.52)	44	2,585	0.29 (0.22-0.40)
	Swedish born	2,449	64,119	1 (Reference)	2,449	64,119	1 (Reference)
				$P_{homogeneity}$ = 0.004 P_{trend} <0.001			$P_{homogeneity}$ = 0.33 P_{trend} = 0.16
	Duration of residence,‡ year						
	<5	25	477	1.12 (0.75-1.66)	30	1,707	0.39 (0.27-0.56)
	5-9	19	324	1.24 (0.79-1.96)	22	1,361	0.33 (0.21-0.50)
	10-19	40	549	1.69 (1.24-2.31)	32	2,084	0.32 (0.22-0.45)
	≥20	46	492	2.09 (1.56-2.81)	30	1,494	0.39 (0.27-0.56)
	Swedish born	2,449	64,119	1 (Reference)	2,449	64,119	1 (Reference)
				$P_{homogeneity}$ = 0.05 P_{trend} <0.001			$P_{homogeneity}$ = 0.79 P_{trend} = 0.21

NOTE: Test for homogeneity and trend was performed as likelihood ratio tests and is made only among foreign-born men with known date of immigration. To assess the homogeneity, we calculated the *P* values for the interaction between country of birth and duration of stay and age at immigration. Tests for trend were performed with the median in each category used as the continuous variable.

*PYRS, person-years at risk divided by 1,000.

†IRRs are adjusted for attained age (2-y intervals except for the age groups 15-20 and 45-54 y) and calendar period of year (2-y intervals except for the 1960-1967).

‡Only among men with known date of immigration. Therefore, weighted average of IRRs presented across the categories of age at immigration and duration of residence are not similar to IRRs presented in Table 2. *Test for homogeneity performed as likelihood ratio tests.

Previous studies have shown that missing family links in the Multi-Generation Register might be a source of bias (18). We repeated our analysis for the period 1991 to 2007, which we have higher quality in this register. The results were not statistically significantly different from the period of 1960 to 2007 and thus not reported.

In an attempt to explore whether the time period before pregnancy to a second-generation immigrant was important, we stratified the analysis among second-generation immigrants by the duration of residence of mothers in Sweden before pregnancy (shorter than 2 y, 2-4 y and 5-9 y, and 10 y or longer). To calculate this duration of residence, we subtracted 1 y from the difference between the first date of immigration of the mother and birth date of the child. Tests for homogeneity and for trend were done as likelihood ratio tests. To assess the homogeneity, we calculated *P* values for the interaction between country of birth and duration of stay and age at immigration. Tests for trend were done with the median in each category used as the continuous variable.

Stratified analysis based on the risk in parental country of birth was done using age-standardized rates (ASR) in countries of birth, derived from GLOBOCAN2002, relative to ASR in Sweden (referred as $IRR_{country\ of\ birth}$). For immigrants with both parents born outside Sweden, we grouped them as the low-risk group if both parents were from areas with an $IRR_{country\ of\ birth}$ of ≤0.8; otherwise, we grouped them as the high-risk group. For immigrants with only one parent born outside Sweden, we grouped immigrants as low-risk group (non-Swedish parent was from areas with an $IRR_{country\ of\ birth}$ of ≤0.8) and high-risk group (non-Swedish parent was from areas with an $IRR_{country\ of\ birth}$ of >0.8). All statistical tests were two sided.

Results

We observed 5,801 cases of testicular cancer during 80 million person-years of follow-up in the cohort. On average, first-generation immigrants had similar (38.9, SD ± 12.1) and second-generation immigrants had lower (34.9, SD ± 12.9) age at exit compared with Swedish-born men (41.0, SD ± 13.4). Mean age at immigration and duration of residence were 24.3 (SD ± 11.3) and 14.4 (SD ± 12.6), respectively.

As shown in Table 1, first-generation immigrants with 530 cases of testicular cancer among 732,228 men during 9.5 million person-years of follow-up had remarkably different IRRs by country of birth. In general, IRRs among first-generation immigrants were reflecting, to some extent, the risk in the countries of birth ($IRR_{country\ of\ birth}$). Compared with Swedish-born men, first-generation immigrants from low-risk countries had a lower risk (IRR 0.43; 95% CI 0.38-0.49) and first-generation immigrants from high-risk countries had a higher risk (IRR, 1.61; 95% CI, 1.42-1.83) of testicular cancer. At the country level, IRR, of testicular cancer was significantly 40% to 85% lower among immigrants born in Ex-Yugoslavia, Lebanon, Finland, Iran, Turkey, and Iraq compared with Swedish-born men. The risk was significantly 40% to 240% higher among men born in Germany, Norway, Denmark, Chile, and Switzerland compared with Swedish-born men.

Table 1 shows the overall risk of testicular cancer among second-generation immigrants with 538 cases during 6 million person-years of follow-up was similar to that of Swedish-born men (IRR, 1.02; 95% CI, 0.93-1.12), but it varied by parental country of birth. An apparent convergence toward the risk of Swedish-born men was observed among most second-generation groups. Compared with Swedish-born men, the risk was significantly 30% to 300% higher among second-generation immigrants whose parents, either one or both, were born in Germany, Poland, Ex-Soviet Union, or Syria.

As shown in Table 2, the risk of testicular cancer among first-generation immigrants with both parents born outside Sweden was significantly lower than Swedish-born men (IRR, 0.67; 95% CI, 0.62-0.74). The risk among first-generation immigrants with at least one parent born in Sweden was similar to that of Swedish-born men (IRR, 0.91; 95% CI, 0.57-1.45). Among first-generation immigrants with both parents born outside Sweden, those from high-risk areas had 60% higher risk, whereas those from low-risk areas showed ~60% lower risk compared with the Swedish-born men.

Among second-generation immigrants, there was no significant difference across parental categories of origin (mother was foreign born, father was foreign born, or both were foreign-born; $P_{homogeneity}$ = 0.94). Second-generation immigrants with both parents born outside Sweden, however, had ~50% higher risk compared with Swedish-born men if parents were from high-risk areas (95% CI, 1.21-1.99) and had ~15% lower risk if parents were from low-risk areas (95% CI, 0.68-1.05).

Comparing to the first-generation immigrants, testicular cancer risk was 30% lower among second-generation immigrants with parents from high-risk areas, whereas the risk was twice higher among second-generation immigrants with parents from low-risk areas (Table 2). When the data were stratified by histopathologic subtypes, the overall results were basically the same but more prominent for seminomas than nonseminomas (Supplementary Fig. S1). At the country level, the risk was significantly higher among second-generation immigrants with at least one parent born in former Soviet Union (IRR, 3.64; 95% 1.01-13.17), Turkey (IRR, 10.63; 95% CI, 3.27-34.61), and Finland (IRR, 1.97; 95% CI, 1.44-2.70) compared with the corresponding first-generation immigrants (Supplementary Table S1).

Table 3 shows IRRs of testicular cancer among first-generation immigrants stratified by age at immigration and duration of residence. In general, the risk decreased by increasing age at immigration and increased by increasing duration of residence regardless of the risk in country of birth. When stratifying the results by histopathologic subtypes, the risk of testicular seminomas was statistically significantly modified by age at immigration

and duration of residence among immigrants from high-risk areas ($P_{homogeneity}$ = 0.004 and 0.05, respectively), but not among those from low-risk areas. The risk patterns in the analysis of risk of nonseminomas were less regular and without statistically significant trend or heterogeneity.

We stratified the data by duration of residence of mothers in Sweden before the pregnancy among second-generation immigrants with mothers born outside Sweden (Table 4). Overall, the risk of testicular cancer among second-generation immigrants was similar to that among Swedish-born men regardless of longevity of residence of their mother in Sweden before pregnancy and regardless of the risk in maternal country of birth.

We found age at peak incidence of seminomas (Fig. 1A) was 5-10 years higher than nonseminomas (Fig. 1B). The age-specific incidence curves were similar for immigrants and Swedish-born men.

Discussion

In this large nationwide cohort study, we found that first-generation immigrants compared with Swedish-born men have a risk of testicular cancer reflecting the risk in their countries of birth—a higher risk if they originated from high-risk areas such as Switzerland, Chile, and Denmark and lower risk if they originated from low-risk areas such as Iran and Turkey. However, the risk in second-generation immigrants was close to the level observed among Swedish-born men and a significant convergence toward the risk in Sweden was observed among second-generation immigrants whose parents were either from low-risk areas or from high-risk areas.

The incidence of testicular cancer has doubled in the past 50 years in several populations, including the United States, Canada, most European countries, and Australia (19-22). Such a rapid increase suggests that environmental and life-style factors are instrumental in the development of testicular cancer. Our findings of a clear maintenance of the risk of the country of birth by first-generation immigrants and the convergence of the risk toward the risk of native Swedes by second-generation immigrants are in line with results of previous studies (7, 23, 24) and provide further evidence of the effect of environmental and life-style factors on testicular cancer risk.

There is a reasonably large amount of epidemiologic and experimental data supporting the hypothesis that factors acting *in utero* play a role in the development of testicular cancer (10). Imbalance in the sex hormones, namely excess estrogens, during pregnancy has been suggested to be instrumental in the etiology of testicular cancer supported by some studies but the results of previous studies diverge and conclusive evidence is lacking (25). Our findings of risk modification of seminomas by age at immigration and duration of residence among first-generation immigrants from high-risk areas, in contrast to the results of previous studies (7, 23, 24), indicate, however, that the risk of testicular cancer is affected by environmental and life-style factors acting postnatal. However, one would

Table 4. IRR and 95% CI of testicular cancer among second-generation immigrants ages 15 to 54 y old in Sweden compared with Swedish-born men by duration of residence of mother before pregnancy and histopathologic subtype, 1960 to 2007

Risk in maternal country of birth	Duration of residence of mother before pregnancy, y	All histopathologic subtypes			Nonseminomas			Seminomas		
		Cases	PYRS*	IRR† (95% CI)	Cases	PYRS*	IRR† (95% CI)	Cases	PYRS*	IRR† (95% CI)
High										
	<2	17	180	1.13 (0.70-1.82)	5	180	0.69 (0.29-1.66)	12	180	1.56 (0.88-2.75)
	2-4	25	223	1.28 (0.87-1.90)	10	223	1.05 (0.56-1.95)	15	223	1.52 (0.91-2.52)
	5-9	20	212	1.01 (0.65-1.57)	11	212	1.11 (0.61-2.00)	9	212	0.91 (0.47-1.76)
	≥10	22	180	1.23 (0.81-1.87)	11	179	1.11 (0.61-2.01)	11	179	1.40 (0.77-2.54)
				$P_{homogeneity}$ = 0.85			$P_{homogeneity}$ = 0.60			$P_{homogeneity}$ = 0.58
Low										
	<2	23	368	0.67 (0.45-1.02)	12	368	0.66 (0.38-1.17)	11	368	0.69 (0.38-1.25)
	2-4	43	423	1.08 (0.80-1.46)	24	422	1.12 (0.75-1.68)	18	422	0.99 (0.62-1.58)
	5-9	37	411	0.95 (0.69-1.31)	17	411	0.79 (0.49-1.28)	19	411	1.10 (0.70-1.74)
	≥10	40	387	1.10 (0.81-1.51)	21	387	1.00 (0.65-1.54)	19	387	1.28 (0.81-2.01)
				$P_{homogeneity}$ = 0.13			$P_{homogeneity}$ = 0.32			$P_{homogeneity}$ = 0.26

NOTE: Test for homogeneity performed as likelihood ratio tests.

*PYRS, person-years at risk divided by 1,000.

†IRRs are adjusted for attained age and calendar period of year. Swedish-born men with both parents born in Sweden were the reference group.

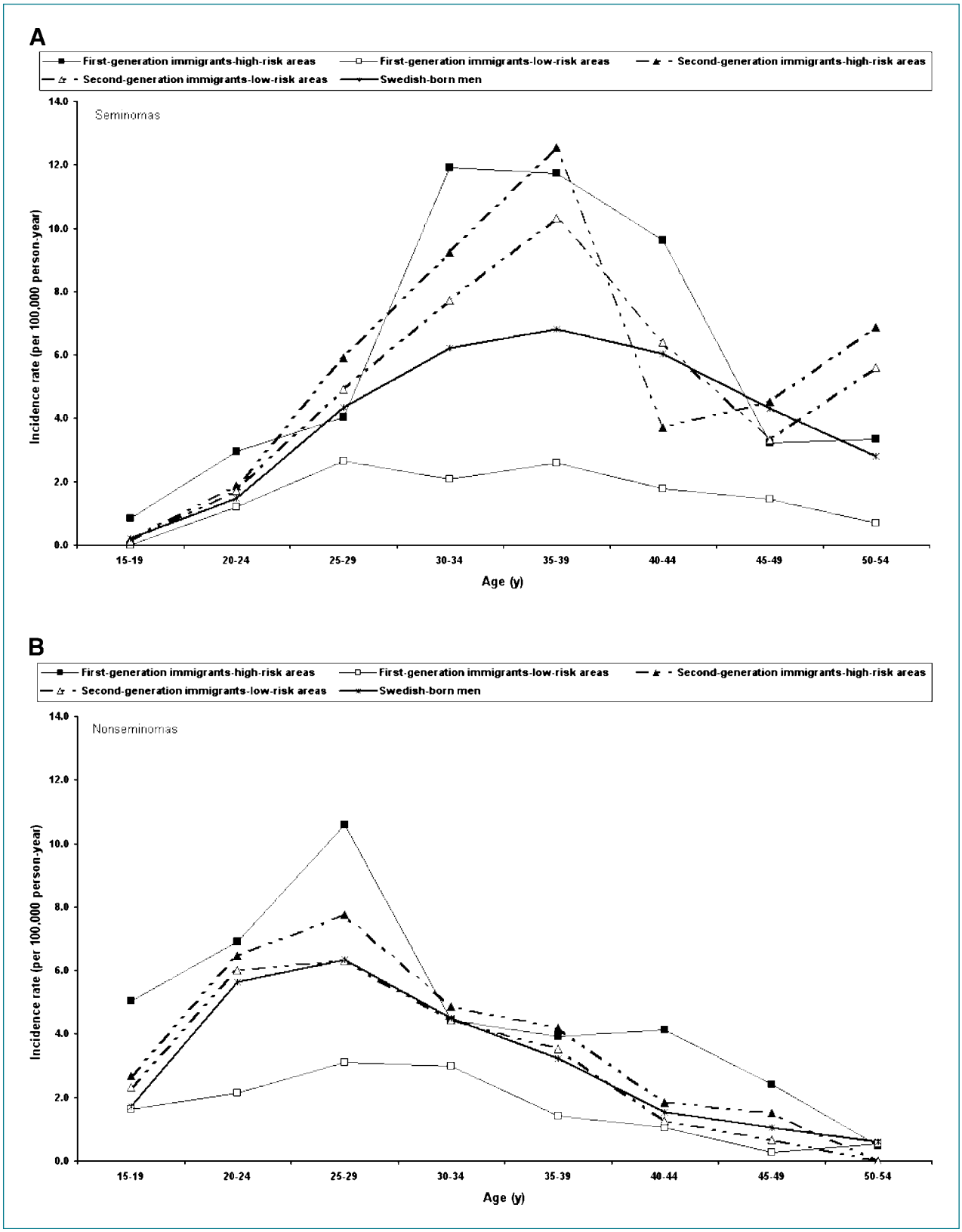

Figure 1. Age-specific incidence rates of testicular cancer seminomas (A) and nonseminomas (B) among immigrants and Swedish-born men ages 15 to 54 y in Sweden by histopathologic subtypes from 1960 to 2007.

think, if postnatal exposures matter, the direction of change in risk would be opposite as to what we observed. Risk should increase with later age at immigration and should decline with longer duration of residence in Sweden relative to their original high-risk environment and exposure to a lower risk environment. There is no clear explanation for this somewhat counterintuitive finding and further investigations would be needed to clarify this.

It should be noted that our finding of risk modification by age at immigration and duration of residence was significant for seminoma tumors among immigrants from high-risk but not among those from low-risk areas. Unfortunately, previous studies supporting the importance of postnatal factors in developing testicular cancer such as the study performed on the effect of age at surgery of undescended testis on the risk of testicular cancer (11) or the study on the risk of contralateral testicular cancer among men with unilaterally undescended testis (12) have not reported risk of testicular cancer separately for seminomas and nonseminomas.

Several risk factors associated with prenatal and perinatal exposures such as birth weight, maternal age, and parity have been suggested for testicular cancer (26-28). We could not adjust for these potential confounders because such information was not available in Swedish registers. However, because these factors can only account for a small fraction of the total incidence and because population in Nordic countries have had very similar pattern of most such factors, differences found in risks among immigrants from Nordic countries could not be explained by these factors (29).

When we stratified second-generation immigrants with both parents foreign born by risk in their parental country of birth, those with parents coming from low-risk areas had a doubled risk compared with first-generation immigrants. Because both the first- and second-generation immigrants were born to foreign-born parents, differences in genetic susceptibility alone are not likely to explain a doubling of the risk. However, the risk of testicular cancer among second-generation immigrants with both parents foreign born and at least one parent from high-risk areas was similar to that of first-generation immigrants. This might indicate the existence of a gene-environment interaction in testicular cancer etiology. There have been some indications of a link between genetic factors and ethnic differences in testicular cancer (30, 31). The direct evidence, however, is lacking. Recently, two genome-wide association studies showed that common genetic variants on chromosomes 12 and 5 are associated with testicular cancer that may partly explain its high incidence in whites (32, 33). Further investigation is needed to combine exposure data with genetic predisposition of testicular cancer.

We found that the risk among second-generation immigrants was similar to that of Swedish-born men in all strata of duration of residence of mother before pregnancy regardless of the risk in maternal country of birth. This finding, not studied earlier, implies that factors associated with testicular cancer etiology are environmental or life-style risk factors that require very short time in the new country to be acquired by mother, given that the hypothesis of importance of *in utero* exposures on the development of testicular cancer is true. This issue need to be further investigated to identify factors that could play a role over the rather short time periods, such as diet, air pollution, and changes in life-style such as smoking.

We found some heterogeneity between the two histopathologic forms of testicular cancer, that is no or modest change in the risk for nonseminomas compared with seminomas. Possibly, the two types do not entirely share risk factors, as suggested by some previous studies (34-37). However, collective evidence from the descriptive literature and marked inconsistencies between analytic studies distinguishing seminomas from nonseminomas indicate that either they are etiological rather than homogeneous, or some heterogeneity exists but the dichotomization is etiologically irrelevant. The findings of gene association studies also suggest that nonseminomas may be worth further investigating for genetic susceptibility (38-42). As nonseminomas comprised diverse subtypes, analysis of nonseminomas by its subtypes may help us to clarify the gene-environment interaction in the etiology of testicular cancer, but few studies will have sufficient numbers for further differentiation.

As applies for almost all migrant studies, the immigrants are not randomly selected from their population of origin and forces of selection probably differ from population to population. This raises the concern about the comparison with country of birth. Follow-up times vary from the different types of immigrants, which is a problem if the etiology of the disease varies by the age of onset. However, we restricted the age to 15 to 54 years. We also reported the risk adjusted for age and calendar period of year among different groups of first-generation immigrants separately.

We obtained ASRs from GLOBOCAN 2002, which estimates incidences based on the available information for each country. Our results for first-generation immigrants from the countries with better cancer registration showed similar or even lower risk compared with the risk in country of birth. However, the risk among immigrants from countries with no or poor quality registers, and low and medium resource countries, showed a higher risk compared with country of birth, indicating that the testicular cancer risk in these countries are likely to be underestimated (3, 4).

The major strength of our study is the unprecedented statistical precision and the population-based design with a long follow-up of all Swedish-born and foreign-born men during the study period. Misclassification with regard to exposure, if any, is most likely independent of testicular cancer and nondifferential because information on exposure was collected before the diagnosis of testicular cancer. Power to stratify the risk among immigrants by histopathologic subtypes, by age at immigration and

duration of residence, and by risk in parental country of birth and the completeness and reliability of registers together with the uniform health care system in Swedish are other strengths (14).

In conclusion, we found that the risk of testicular cancer was lower than that of Swedish-born men for first-generation immigrants from low-risk countries and was higher for first-generation immigrants from high-risk countries. We also found that the risk of testicular cancer reflects the risk in the countries of birth, whereas the risk in second-generation immigrants was similar to that in Swedish-born men. These findings together with the observation of risk modification by age at immigration and duration of residence provide important clues for future studies of testicular cancer etiology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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