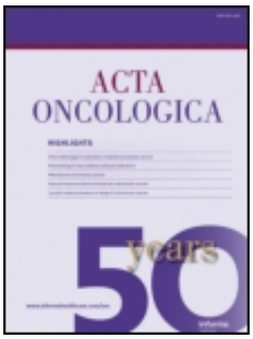

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ORIGINAL ARTICLE

Testicular cancer risk according to county of birth and county of diagnosis in Norway, 1958–2007

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Abstract

Background. The etiology of testicular germ cell cancer (TGCC) is still poorly understood, but biological and epidemiological evidence suggest that TGCC originates early in life. The aim of the present study was to analyze heterogeneity in TGCC risk within Norway, comparing county of birth to county of diagnosis, in order to assess the relative contribution of risk factors acting early and later in life. A further aim was to present the Norwegian TGCC incidence rates (1958–2007). *Material and methods*. All TGCC cases (n = 7130) reported to the Cancer Registry of Norway, 1958–2007, were analyzed by county of diagnosis in 10-year intervals. The relative risk of TGCC based on county of birth, was estimated by Poisson regression analysis of all new TGCC cases (n = 1943), based on the mother's county of residence at the time of the son's birth, 1967–2007, obtained by linkage between the Cancer Registry and the Medical Birth Registry of Norway. *Results*. Between the first (1958–67) and last (1998–2007) 10-year period, the average incidence rate more than tripled from 3.3 to 10.5 per 100 000 person-years (world adjusted), respectively. The average incidence rate during 1968–2007 was highest in the county of Rogaland (8.6) and lowest in Hedmark (5.3), the ratio between them being 1.6. The relative risk of TGCC based on county of birth (1967–2007) varied between 1.43 (Møre og Romsdal) and 0.95 (Buskerud), giving a ratio of 1.5. *Conclusions*. The ratio between the relative risk in the highest and lowest county was basically similar when comparing counties of birth with counties of diagnosis. Thus, our data do not shed light on the relative contribution of risk factors acting early versus later in life. The incidence rate of TGCC in Norway is among the highest in the world, and the increase in incidence rate does not seem to level off.

The incidence of testicular germ cell cancer (TGCC) has increased rapidly in almost all European populations during the last decades [1], and there are considerable differences depending on country of diagnosis, birth cohort and ethnicity [2–4]. Norway and Denmark are among the countries with the highest incidence rates of TGCC in the world, but in the neighboring countries Sweden and Finland the rates are by comparison only about half and one third, respectively [4].

The etiology of TGCC is poorly understood, but biological and epidemiological evidence suggest that testicular carcinogenesis is initiated in the early stage of life, possibly *in utero* [5–7]. Therefore, temporal and spatial differences in exposure to environmental factors acting early in life are suspected. Estrogens (including xenoestrogens) and environmental antiandrogens are among the compounds being investigated [8 –10]. Genetic susceptibility is also of importance since brothers of TGCC cases have an eight- to ten-fold excess risk of developing the disease, while the relative risk to fathers and sons of TGCC cases is increased about four-fold [11]. Since the increase in incidence rate has been so rapid, an interaction between genetic and environmental factors is likely.

Large differences in TGCC incidence exist not only between the Nordic countries [2], but also within them. A comparison of the incidence rates of TGCC, diagnosed in the 1970s, demonstrated a large variation within the Nordic countries, assessed as the ratio between the incidence rate in the county with the highest and the lowest incidence rate within each country [12]. This ratio varied between 2.0

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(Denmark) and 3.9 (Finland), implying that relevant regional differences also exist within the various Nordic countries.

This issue was further explored by Møller, who showed that the geographic pattern of incidence in Denmark is stronger for the area of childhood residence than for the area of residence at the time of diagnosis [13]. This indirectly supports the notion that TGCC is caused by unidentified factors early in life as opposed to later in life. A more recent study has also demonstrated a significant heterogeneity in the risk of TGCC according to birthplace and birth cohort in Denmark, the geographical variation being several-fold [14]. Similarly, claims have been made that TGCC risk in Norway was associated with growing up on a farm, particularly if specific fertilizer regimens were used [15]. On this background, the present study was designed to analyze heterogeneity in TGCC risk within Norway, comparing county of birth to county of diagnosis, in order to gain more insight into the relative contribution of risk factors acting early in life, and those exerting their effect later in life. Another aim was to present the most recent incidence rates for Norway as a whole and for the various counties.

Material and methods

In Norway there are 19 counties, shown in Figure 1, including average TGCC incidence rates for the most recent 10-year period (1998–2007). The island of Svalbard is part of Norway, but its population (currently of about 2600) was considered too small to be included in the analyses.

The data analyzed in this study were obtained from the Cancer Registry of Norway which was established in 1951. The registry is based on compulsory reporting of all new cancer cases in the Norwegian population since 1953. Testicular cancer is a disease which is unlikely to remain undiagnosed, and the quality of acquired data in the registry is considered to be high. Some misclassification between germ- and non-germ cell tumors as well as seminomas versus non-seminomas has likely still occurred. Site and morphology have been coded according to ICD-O-2 since 1993. Before 1993, site was coded according to ICD-7, while the morphology was coded according to a modified version of SNOMED [4].

Data were also obtained from the Medical Birth Registry of Norway, which was established in 1967 and covers all live births and still births with a gestational age above 16 weeks. After acquiring the necessary permissions, data from these two registries were linked in order to identify the mother's county of residence at the time of the son's birth, from the year 1967 onwards. We consider this to be a good proxy variable for the mother's county of residence during first trimester of the pregnancy, data of which are not readily available.

All reported TGCC cases in Norway were analyzed by county of diagnosis in 10-year intervals from 1958 to 2007. Data from 1953–1957 were excluded both to simplify the analyses, and because the data collected during the first few years may have a higher risk of being incomplete. The same data were used to assess the frequency and distribution of bilateral TGCC.

The relative risk of TGCC was estimated by Poisson regression analysis performed for all new cases, born 1967–2007, based on the mother's county of residence at the time of the son's birth, and adjusted for age at diagnosis. For this analysis, the capital of Oslo along with the counties of Akershus and Hordaland, were chosen as the reference population *a priori*. These areas are relatively densely populated, containing about 32% of the Norwegian population in 2009 [16]. In addition, these areas have traditionally had the largest numbers of immigrants from other parts of Norway. The same data were used to assess the frequency and distribution of brothers with TGCC.

A calculation of what the present data provide in terms of power to detect a difference between the relative risk in the highest and lowest county, comparing counties of birth with counties of diagnosis, was performed based on the approach outlined by Isabel dos Santos Silva [17]. Preliminary results have shown that the relative risk between the highest and lowest county of birth is 1.5, based on 145 and 77 incident cases in the county with the highest and lowest risk, respectively. We estimated a power of 75% to detect a reduction in rate ratio from 1.5 (based on county of birth) to 1.0 (based on county of diagnosis), with a p-value of 0.05. This is the most extreme change one could theoretically achieve and does not require any assumption of a specific moving proportion. Since 75% is the lowest acceptable power, and a much smaller risk reduction than from 1.5 to 1.0 is what could be anticipated, the power in our material is too low to detect a realistic difference between the relative risk in the highest and lowest county, when comparing counties of birth with counties of diagnosis. Still our point estimates of the relative risk in the counties of birth and diagnosis are likely to give an indication of what can be achieved by this approach, although firm conclusions cannot be made.

Results

From 1958 to 2007, 7412 new cases of invasive testicular cancer were reported in Norway. Of these, 42

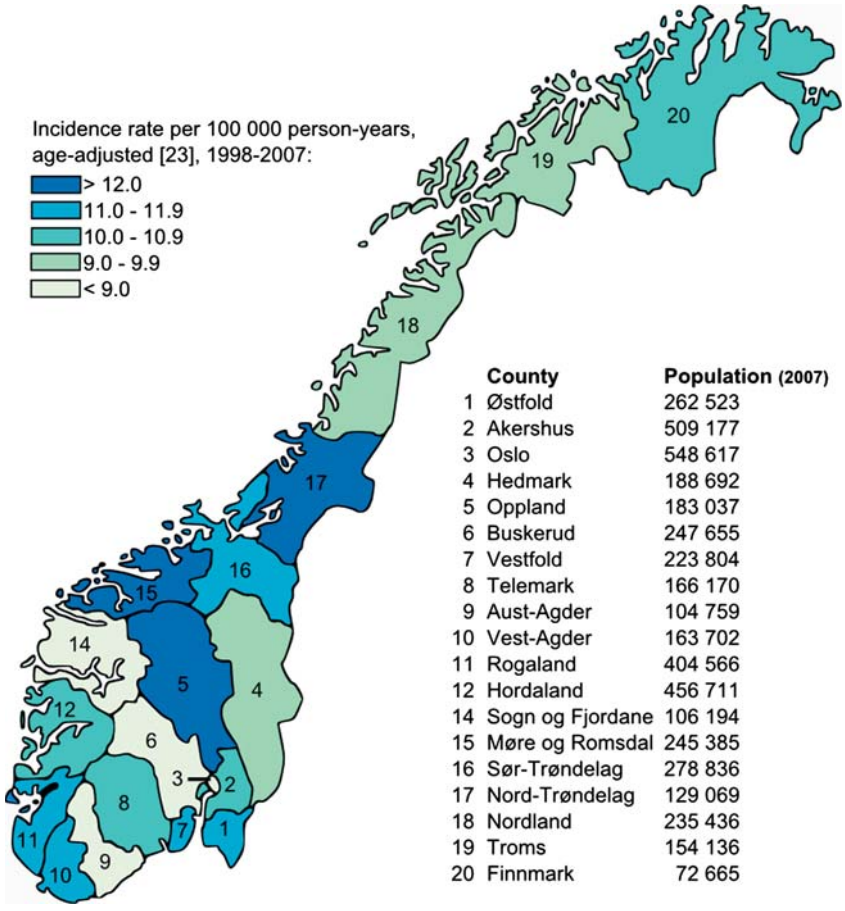

Figure 1. Average annual incidence rate of testicular germ cell cancer (per 100 000 person-years, age-adjusted using the world standard [23]) in Norway by county, 1998–2007 [24], with corresponding population size (2007).

cases were not histologically verified and were excluded from analysis. Seven men who had the disease as an incidental finding at autopsy, were also excluded. Cases of non-germ cell tumors (such as sarcomas and lymphomas) were not included in the analysis. In addition, all spermatocytic seminomas reported in 1993 or later were excluded as these are not considered to be true germ cell tumors. Most of the spermatocytic seminomas diagnosed before 1993 were also excluded, although the exact number is not known because of the way the disease coding was done at the time. In total, 7130 histologically verified TGCC cases were analyzed, including 82 persons with a non-classified TGCC. If a person had developed bilateral TGCC, only the first case is reported here. The results are presented in Table I. The average incidence rates for the four last 10-year periods (1968–2007) were calculated with the specific purpose of being compared with the relative risk estimates of the Poisson regression analysis based on the county of birth (see below). The ratio between the county with the highest (Rogaland) and the lowest (Hedmark) incidence rates, 8.6 and 5.3 per 100 000 person-years (world adjusted), respectively, was 1.6.

Between 1958 and 1967, 604 new TGCC cases were reported in Norway. This number had risen to 2522 between 1998 and 2007, more than tripling the average incidence rate from 3.3 to 10.5 (Table I). On average, there has been a 34% increase in this rate from one 10-year period to the next, showing few signs of stagnation. During the most recent 10-year period, 1998–2007, Nord-Trøndelag was the county with the highest incidence rate (13.7), with Møre og Romsdal (13.4) not far behind. The rate in Nord-Trøndelag was about 30% higher than the national average and about 76% higher than in Sogn og Fjordane, where the incidence rate of TGCC was the lowest (7.8).

Using the same data and time intervals as in Table I, the incidence rates of invasive TGCC stratified by age are given in Table II. The incidence rate of TGCC has increased in all age groups during 1958–2007. The largest absolute increase has been in the 25–34 years age group, i.e. 9.7 and 29.5 per 100 000 person-years (world adjusted) in the first and last 10-year period, respectively, and TGCC was also most commonly diagnosed in this age group. The smallest relative increase during 1958–2007 has been among males older than 54 years.

Table I. Number of new testicular germ cell cancer and adjusted annual average incidence rates (per 100 000 person-years, age-adjusted using the world standard [23]) in Norway and each county, 1968–2007, and in 10-year intervals, 1958–2007.

	Years of diagnosis						
	1958–1967	1968–1977	1978–1987	1988–1997	1998–2007	1968–2007	Increase in IR (%) and 95% CI*
County of diagnosis	Number of new cases/adjusted average incidence rates						
Norway (total)	604/3.3	834/4.3	1293/6.0	1877/8.0	2522/10.5	6526/7.3	34 (33–36)
Reference population**	187/3.5	261/4.4	420/6.4	574/7.7	811/10.0	2066/7.3	30 (27–34)
Ostfold	27/2.8	44/4.2	60/5.0	108/8.6	146/11.2	358/7.3	41 (36–47)
Akershus	41/2.9	86/4.8	130/6.3	179/7.8	254/10.3	649/7.4	35 (29–41)
Oslo	88/3.8	105/4.4	162/6.7	205/7.3	297/9.0	769/7.0	25 (19–31)
Hedmark	25/2.8	25/2.6	37/4.2	45/4.5	88/9.8	195/5.3	36 (20–52)
Oppland	32/4.1	40/4.6	52/5.6	91/9.2	112/12.7	295/8.1	34 (26–43)
Buskerud	26/2.7	42/4.3	63/5.7	89/7.2	102/8.3	296/6.4	31 (25–38)
Vestfold	24/2.9	37/4.1	56/5.8	85/8.0	119/11.1	297/7.4	40 (40–41)
Telemark	29/4.2	39/5.2	49/6.4	64/7.6	83/10.0	235/7.2	24 (22–25)
Aust-Agder	11/2.8	12/3.0	24/5.0	36/7.2	44/8.1	116/6.1	35 (27–43)
Vest-Agder	23/4.2	24/3.8	50/7.1	62/8.0	91/11.0	227/7.7	31 (21–41)
Rogaland	35/2.9	50/3.7	136/8.0	176/9.2	239/11.4	601/8.6	44 (32–56)
Hordaland	58/3.6	70/3.8	128/6.2	190/8.2	260/10.8	648/7.5	35 (28–41)
Sogn og Fjordane	16/3.0	25/5.2	27/4.9	44/8.0	43/7.8	139/6.5	27 (15–38)
More og Romsdal	33/3.3	46/4.1	72/5.9	132/10.4	168/13.4	418/8.5	45 (39–51)
Sor-Trondelag	35/3.0	61/5.3	82/6.3	99/7.0	154/11.0	396/7.4	33 (24–42)
Nord-Trondelag	25/4.4	23/4.1	34/5.1	57/8.4	87/13.7	201/7.9	35 (21–50)
Nordland	48/3.8	56/4.6	64/5.0	102/7.8	117/9.6	339/6.7	27 (20–33)
Troms	22/3.4	34/4.7	46/5.5	84/9.7	79/9.7	243/7.4	33 (24–41)
Finnmark	6/1.5	15/3.6	21/4.6	29/6.3	39/10.6	104/6.1	57 (44–69)

*Average increase in incidence rate (IR) between each 10-year period, as percentage (%) and 95% confidence interval (CI).
**Number of new cases in the counties of Oslo, Akershus and Hordaland combined.

When differentiating between seminomas and non-seminomas, we excluded 82 cases where a non-classified TGCC had been reported. The total number of cases to be analyzed was therefore 7038. In total, 3762 of these cases (54%) were seminomas, and the remainder were non-seminomas and cases of mixed histology. Figure 2 shows the incidence rates stratified by age (above 14 years) and time period of diagnosis. It further underscores that the greatest increase has taken place among those aged 25–34 years, and that seminomas are, on average, diagnosed at a higher age than non-seminomas.

Among 1.2 million men born 1967–2007, and hence with a medical birth registry record, 1945 cases of TGCC had been registered as of 31 December, 2007. Of these, two cases were excluded from analysis due to incomplete information. The relative risks of TGCC, estimated by Poisson regression analysis based on the mother's county of residence at the time of the son's birth, are given in Table III. Being born to a mother living in the counties of Sør-Trøndelag, Møre og Romsdal, Oppland or Østfold at time of delivery, was associated with a significantly higher risk of developing TGCC compared to the reference population ($p < 0.05$). Of these, Møre og Romsdal was associated with the highest risk, about 40% higher than the reference population. The ratio between the relative risk estimate pertaining to the county with the highest and the lowest risk, respectively, Møre og Romsdal (1.43) and Buskerud

Table II. Annual average incidence rates of testicular germ cell cancer (per 100 000 person-years, age-adjusted using the world standard [23]) in Norway, 1958–2007, and in 10-year intervals, stratified by age.

Age (years)	1958–1967	1968–1977	1978–1987	1988–1997	1998–2007	1958–2007	Increase in IR (%) and 95% CI*
0–14	0.2	0.3	0.3	0.5	0.5	0.4	24.5 (18.4–30.6)
15–24	2.4	4.4	7.9	11	13.2	7.8	54.8 (47.5–62.1)
25–34	9.7	9.5	15.6	22.6	29.5	18.4	36.3 (31.6–41.0)
35–44	7.1	9.8	11	13.3	20.3	12.6	27.3 (25.6–29.0)
45–54	3.3	5.4	6.2	7.1	9.5	6.5	26.8 (24.1–29.5)
55+	1.9	2	2	2.8	2.8	2.3	12.3 (10.8–13.8)
All (crude)	3.3	4.2	6.3	8.8	11.1	7.0	37.0 (35.0–39.0)
All (adjusted)	3.3	4.3	6	8	10.5	6.6	34.0 (32.5–35.5)

*Average increase in incidence rate (IR) between each 10-year period, as percentage (%) and 95% confidence interval (CI).

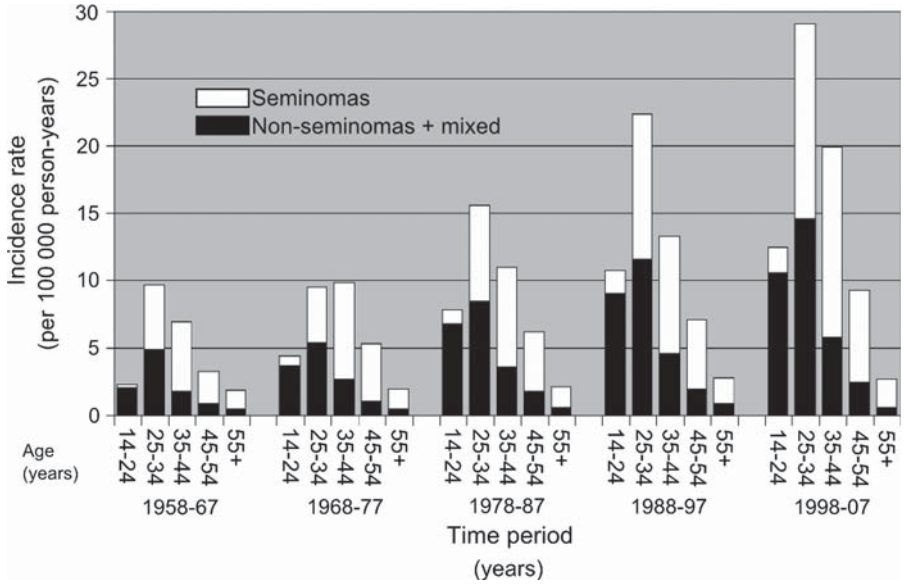

Figure 2. Incidence rate of testicular germ cell cancer (per 100 000 person-years, age-adjusted using the world standard [23]) in Norway, 1958–2007, by age and histology.

(0.95), was 1.5. This ratio was thus comparable to the corresponding ratio of relative risk estimates based on county of diagnosis (Table I).

Comparing county of birth with county of diagnosis showed that, among the 1943 TGCC cases, 1372 were still living in the county where they were born, yielding a moving proportion of 29%. The majority of those who moved, settled in a neighboring county.

The medical birth registry data revealed that there were 17 pairs of brothers with TGCC having the same mother, and in addition there was a family with three affected brothers (altogether 37 cases). The brother cases were quite evenly spread throughout the counties. A clear exception was seen in Finnmark, where eight of these 37 cases (22%) were born even though only 2.1% of male births and 2.5% of TGCC cases have been reported from Finnmark for these birth cohorts (data not shown). From 1958 to 2007, 214 bilateral cases have been registered. On a national level, a contralateral tumor has developed in 3.2% of the cases. The counties of Buskerud and

Table III. Relative risk of testicular germ cell cancer (TGCC), estimated by Poisson regression analysis on a county level based on the mother's county of residence at the time of the son's birth, adjusted for age at diagnosis.

Mother's county of residence at son's birth	Number of male births 1967–2007	Incident cases of TGCC	Relative risk estimates and 95% CI*
Reference population**	373171	527	1 (referent)
Ostfold	58660	116	1.33 (1.08–1.62)
Hedmark	41711	64	1.01 (0.78–1.31)
Oppland	42794	88	1.34 (1.07–1.68)
Buskerud	55763	77	0.95 (0.74–1.20)
Vestfold	48794	88	1.23 (0.98–1.54)
Telemark	40150	75	1.22 (0.96–1.55)
Aust-Agder	24986	43	1.17 (0.85–1.59)
Vest-Agder	41479	69	1.13 (0.88–1.46)
Rogaland	106126	168	1.12 (0.94–1.33)
Sogn og Fjordane	29834	48	1.07 (0.79–1.43)
More og Romsdal	66243	145	1.43 (1.19–1.71)
Sor-Trondelag	72010	131	1.22 (1.01–1.48)
Nord-Trondelag	34314	63	1.20 (0.93–1.56)
Nordland	67025	115	1.09 (0.89–1.39)
Troms	44851	78	1.14 (0.90–1.44)
Finnmark	24910	48	1.22 (0.91–1.64)
TOTAL	1172821	1943	

*Regression coefficients from the Poisson regression analysis and 95% confidence interval (CI).
**The counties of Oslo, Akershus and Hordaland combined.

Nord-Trøndelag have a significantly higher percentage of bilateral cases than the national average, while the percentage was significantly lower in Oppland, Finnmark and Akershus. There was no significant correlation between the percentage of bilateral cases and the incidence rate of TGCC in the various counties (data not shown).

Discussion

The most convincing epidemiologic evidence suggesting that TGCC originates early in life, has been provided by population migration studies. It has been shown that men emigrating from countries with high incidence of TGCC to countries with a low incidence, or vice versa, maintained the risk of their home country, irrespective of their age at immigration. The risk among second-generation immigrants was similar to the risk in the country their parents migrated to [6,7]. For similar reasons, it has been anticipated that the heterogeneity in TGCC risk is greater between counties of birth than between counties of diagnosis. The observation that geographic pattern of incidence in Denmark was stronger for the area of childhood residence than for the area of residence at the time of diagnosis, is concordant with this notion [13]. The present study, however, based on Norwegian population-based data from the Cancer Registry and the Medical Birth Registry, did not reveal any difference in heterogeneity in the relative risks between counties of birth compared to counties of diagnosis, covering the period 1968–2007. The results thus do not provide any evidence supporting the belief that TGCC is related to risk factors exerting their effect early as opposed to later in life.

TGCC is a disease largely affecting males between 20 and 45 years of age. Since most people who move, tend to do so in their 20s or 30s, the number of years they are being exposed to a new environment before eventually acquiring the disease, is likely to be few. Furthermore, the tendency for people moving from the countryside to the cities, is also not thought to represent a major change in risk as there has never been a consistent TGCC risk gradient between peripheral and central areas of Norway [18]. The smaller the fraction of people moving before they eventually are being diagnosed with TGCC, the smaller the dissipation of the gradient between counties of birth and those of diagnosis may be expected.

The moving proportion of 29% was based on a comparison of county of birth and county of diagnosis for the 1943 TGCC cases we had birth data on, and may seem as a low number. This way of measuring moving proportion is, however, a "fewest case scenario" as it conceals that many people who are registered with identical birth and diagnosis counties might still have had residence in another county for years (i.e. returning to the birth county after finishing an education). Also, the analysis is dependent upon people having an updated home address at time of diagnosis, something which not all people (especially younger) tend to have, particularly if they intend to return after a relatively short time period. We believe that the moving proportion is likely to be sufficiently high to dissipate some of the gradients possibly present if the various counties pose a different risk for the offspring during pregnancy.

It was known beforehand that the power in our material was too low to detect a realistic difference between the relative risk in the highest and lowest county, when comparing counties of birth with counties of diagnosis. There was however no way to expand our study sample as information on all available births in Norway since 1967 was included. It was reasoned that our point estimates of the relative risk in the counties of birth and diagnosis would still be likely to give an indication of what can be achieved by this approach, although firm conclusions cannot be made. In addition, the overall idea of the study was regarded as interesting from an epidemiological and biological point of view and thus worthwhile pursuing.

The variation in incidence rates between Norwegian counties seems to be lower than in Denmark; and the lower the rates, the lower the probability of detecting possible differences between counties of birth compared to those of diagnosis. As mentioned, we are not able to conclude whether such differences exist, but if they do, they are likely to be small. An explanation for the small difference in rates could be that the Norwegian population is relatively homogenous with regard to genetic susceptibility, and/or that any environmental risk factors are more evenly distributed in Norway than in other countries, such as Denmark.

One could argue that it would have been worthwhile to study specifically the various environmental risk factors related to the different counties. There is however not sufficient information available for this kind of analysis, which is why the county specific rates have been used only as a measure of the variation between the counties. This also explains why a different combination of counties is compared when we are looking at counties of birth and counties of diagnosis.

The actual comparison between the risk related to county of diagnosis and county of birth, was based on different study populations. The incidence rates pertaining to the counties of diagnosis were based on a heterogeneous group of people. Although being diagnosed in a relatively narrow time window from

1968 to 2007, they were born during a long time period, thus reflecting TGCC cases with a range of different exposures, age at diagnosis and moving histories. The strength of these data, however, is that they are population-based and thus provide the best possible and robust risk estimates of the respective county, covering the whole period during which the TGCC cases we have medical birth registry data on, were born.

Bilateral cases and familial cases among brothers were also included, as these groups can be assumed to be particularly genetically susceptible. The brother cases are quite evenly spread throughout the counties, apart from in Finnmark, where there seems to be a clustering of brother pairs with TGCC. Whether this is due to random genetic clustering or local environmental factors is unknown, but it seems unrelated to the risk of developing unilateral or bilateral TGCC. If anything, the relationship seems to be inverse, since Finnmark is one of the counties with significantly less occurrence of bilateral cases than the remaining ones. The county-specific TGCC risk does not correlate with the number of brother pairs, nor to the percentage of bilateral cases. This may indicate that susceptibility involving multiple low-penetrance genes rather than clustering of high-penetrance genes, acting in combination with environmental factors, are responsible for the current epidemiologic pattern of TGCC. However, the total number of both bilateral cases and affected brother pairs was low, thus making it difficult to draw firm conclusions.

This study shows that the incidence rate of TGCC in Norway is among the highest in the world (10.5 per 100 000 person-years on average during 1998–2007), and also suggests a further increase compared to 1998–2002 average rates reported by IARC previously (9.6 per 100 000 person-years) [4]. The incidence rates presented here may be slightly lower than those found in comparable reports because we attempted to exclude all non-germ cell cancer cases from analysis. The finding that about 3% of TGCC cases have become bilateral on a national level, is comparable to what has been reported in other studies (about 2–5%) [19,20]. This is also the case for the distribution of seminomas vs. non-seminomas in the different age groups.

Although the incidence rates were not monotonically increasing in all counties throughout the observation period, this is unlikely to be attributed to a possible leveling off of the increasing trends. Such indication has been observed in Switzerland and some other countries [21,22], but for a small population like the Norwegian, the observed scatter in county rates is most likely due to random variation. However, the elevated TGCC rates in the county of Møre og Romsdal has raised some concern that chemical compounds used in furniture or maritime industry are parts of the cause of the increased risk by being born to a mother living in that county, as these forms of industry have been common in parts of the county for decades. The difficulties in pursuing such an hypothesis, however, is the rarity of the disease, lack of specific exposure estimates, and the long follow-up that is required.

In conclusion, we did not observe any heterogeneity in TGCC risk within Norway when comparing county of birth to county of diagnosis. Our data thus do not shed light on the relative contribution of risk factors acting early in life, and those exerting their effect later in life. An explanation for the small difference in rates could be that the Norwegian population is relatively homogenous with regard to genetic susceptibility, and/or that any environmental risk factors are more evenly distributed in this country as compared to other countries. The incidence rate of TGCC in Norway is among the highest in the world, and the increase in incidence shows few signs of stagnation.

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