A population-based study of testicular cancer risk among children and young adults from Norway and Utah, USA

Ruby Del Risco Kollerud[a,b*], Hege S. Haugnes[c,d], Bjørgulf Claussen[a], Magne Thoresen[e], Per Nafstad[a] , James M Farnham[f], Karl Gerhard Blaasaas[g], Øyvind Næss[a], Lisa A. Cannon-Albright[f].

[a]Institute of Health and Society, University of Oslo, P.O Box 1130 Blindervn, 0318 Oslo, Norway
[b]The National Centre for Occupational Rehabilitation in Norway. Haddlandsvegen 20, 3864 Rauland, Norway
[c]Department of Oncology, University Hospital of North Norway, Tromsø
[d]Institute of Clinical Medicine, UIT- The Arctic University, Tromsø, Norway
[e]Department of Biostatistics, Oslo Centre for Biostatistics and Epidemiology, University of Oslo, Norway.
[f]Genetic Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, 84108 USA.
[g]Finance Norway, P.O Box 2473 Solli, 0202, Oslo Norway

* Corresponding author. Tel.: +4747970236; fax: +4735 07 32 68
E-mail address: ruby.kollerud@hotmail.com

Novelty and Impact
A clear difference in testicular cancer incidence among individuals born in Norway and descendants of Scandinavian people born in Utah was observed. Norwegian males born between 1980 and 1984 had twice the testicular cancer incidence found in Utah in the same period.
These differences in testicular cancer rates point to the possibility of environmental influences and/or lifestyle factors.
Family history of testicular cancer is a strong risk factor for developing testicular cancer in both populations.

Abbreviations
TC: testicular cancer
UPDB: Utah Population Database
DSF: the Norwegian National Population Register
UCR: the Utah Cancer Registry
NCI: National Cancer Institute
SEER: the Surveillance, Epidemiology, and End Results
ICDO-3: International Classification of Diseases for Oncology
HR: hazard ratios

Abstract

Similar family-based cancer and genealogy data from Norway and Utah allowed comparisons of the incidence of testicular cancer (TC), and exploration of the role of Scandinavian ancestry and family history of TC in TC risk.

This study utilizes data from the Utah Population Database and Norwegian Population Registers. All males born during 1951-2015 were followed for TC until the age of 29 years. A total of 1,974,287 and 832,836 males were born in Norway and Utah, respectively, of whom 2,686 individuals were diagnosed with TC in Norway and 531 in Utah. The incidence per year of TC in Norway (10.6) was twice that observed in Utah (5.1) for males born in the last period (1980-1984). The incidence rates of TC in Utah did not differ according to presence or absence of Scandinavian ancestry (p=0.669). Having a brother diagnosed with TC was a strong risk factor for TC among children born in Norway and Utah, with HR= 9.87 (95% CI 5.68-17.16) and 6.02 (95% CI 4.80-7.55), respectively; with even higher HR observed among the subset of children in Utah with Scandinavian ancestry (HR=12.30 95% CI 6.78- 22.31).

A clear difference in TC incidence among individuals born in Norway and descendants of Scandinavian people born in Utah was observed. These differences in TC rates point to the possibility of environmental influence. Family history of TC is a strong risk factor for developing TC in both populations.

Keywords
Testicular cancer, testis, testicular cancer incidence, germ cell tumour, familial aggregation, family history, familial risk, UPDB, children.

1. Introduction

Germ-cell testicular cancer (TC) is the most frequent solid cancer among young Caucasian males.[1] For unknown reasons, the incidence of TC has increased substantially in many countries during the last five decades, with the highest incidence found in Denmark and Norway.[2,3] In several countries, incidence trends of TC are consistent with birth-cohort effects, suggesting that any risk factor associated with increased incidence would vary with birth cohorts.[4] A cohort effect occurs when different distributions of disease arise from a changing or new environmental cause affecting age groups differently. [5]

The aetiology of TC remains largely unknown. A family history of TC and other cancers is a strong risk factor for TC.[6] A recent study found evidence for a moderate penetrance TC susceptibility gene. However, specific high-penetrance susceptibility genes predisposing to TC have not been identified.[7,8] Moreover, recent studies show that genetic susceptibility for the risk of TC is mediated by more than 50 susceptibility loci, each providing a low or moderate risk.[9],[10]

The risk factor most consistently associated with TC is cryptorchidism, which together with additional disorders of the male reproductive system including hypospadias and impaired spermatogenesis have been grouped into the Testicular Dysgenesis Syndrome.[11] Considering that TC peaks in incidence among young men of reproductive age it is believed that high oestrogen levels in utero may contribute to the development of TC (the oestrogen hypothesis, Sharpe and Skakkebaek, 1993).[12] The so-called oestrogen hypothesis has been expanded to include also environmental antiandrogens as endocrine disrupters with potential adverse effect on male reproductive health. [13] However, relatively few chemicals have so far been closely examined for their possible hormone activity in humans.

In the latter half of the 19th century and the first decades of the 20th century, over one million Scandinavians emigrated to America; some were members of the Latter-Day Saints church from the Mormon Scandinavian Mission.[14,15,16,17] They had many of the same motives as other migrants, but in addition they were directly encouraged to settle in Utah where most of the population still practices the Mormon religion. This population is well-known for their lifestyle characteristics including large family size, a healthy lifestyle, and proscriptions against alcoholic beverages and tobacco.[18] Children born in Utah with Scandinavian ancestry

will share genes with people from Scandinavian countries, but they have grown up in different environments. The increase and high incidence of TC in Norway may be caused by genetic and/or environmental factors. For the purpose of investigating the roles of genetic and environmental factors we used triangulation, integrating two different methods to analyse data.[19] We investigated TC cancer incidence in children born in Utah with Scandinavian ancestors as a means to evaluate the impact of the Utah environment on cancer risk and the potential timing of an environmental factor. In addition, we also explored family history of cancer as indicator for a possible environmental and/or genetic influence. Using data from the *Utah Population Database* (UPDB) and *the Norwegian National Population Register* (DSF), we were able to conduct a unique comparison of incidence and family history of cancer in Utah and in Norway. The aim of this study was to

1) explore and compare TC incidence in males <30 years born in Norway and Utah, taking Scandinavian ancestry into account
2) explore trends of TC incidence over time
3) evaluate the risk of developing TC with regard to family history of TC.

2. Materials and methods

2.1 Study population

All males born during 1951-2015 in Norway and Utah who were also registered in UPDB or DSF were included in the study. The UPDB is one of the world's richest sources of linked population-based information and contains data for over 9 million individuals and their descendants from the late 18th century to the present. It was originally constructed based on data provided by the Genealogical Society of Utah and is kept current with state vital statistics data.[20] The Norwegian DSF has information on the relationship between each individual person and his/her relatives. Every person in the register has a Norwegian personal identification number which makes it possible to link the person with other registries. These databases enable us to follow all individuals from birth to death, end of study or emigration. Regarding emigration from Utah we used the last known date of residence, which is determined by when the individual had an event recorded in Utah from vital records (deaths, births, adoptions, marriages, divorces, Utah driver's license registration and renewal, voter registration, census data and state-wide inpatient and ambulatory care).

2.2 Cancer cases

Cancer cases among all included males and their relatives were identified through linkage of the two databases to cancer registries, the Utah Cancer Registry (UCR), an NCI Surveillance, Epidemiology, and End-Results (SEER) Registry from 1973, which includes all independent primary cancer diagnoses for Utah residents from 1966 through 2015, and the Norwegian Cancer Registry, which was initiated in 1953. [21,22] By law, all incident cancer diagnoses must be reported to both registries.

Cases or index persons were all males diagnosed with TC before the age of 30 between 1953 and 2015 in Norway and between 1966 and 2015 in Utah. TC was classified into seminomas and non-seminomas using the International Classification of Diseases for Oncology (ICDO-3) and topography (C62). (Appendix 1). Family history of TC was classified according to the ICD-10 (Appendix 1).

2.3 Scandinavian ancestry

In the UPDB we defined ancestry as an individual's ethnic origin, or place of birth of an individual's ancestors prior to arrival in Utah. To compare ancestry groups, we split the population in Utah into children with Scandinavian ancestry and children with non-Scandinavian ancestry. Appendix 2 describes the method used for the identification of Scandinavian ancestry.

2.4 Statistical analysis

Incidence rates of TC with 95% confidence intervals (CI) for seven 5-year birth cohorts were calculated for individuals born between 1951 and1984, to allow the same time frame (until the age of 30) for each individual to develop TC. The rates were calculated by dividing the total number of TC cases in each cohort by the total number of follow-up years multiplied by 100,000. A Poisson model was used to evaluate whether TC incidence had changed over time.

We present TC incidence rates for the population aged 0-29 years in Norway and Utah, and according to Scandinavian ancestry.

To analyse the impact of family history of TC on risk of TC, we used stratified Cox regression, where each birth cohort (10-year time period) was entered as a separate stratum. Using this approach, we could control for secular trends in the disease and birth-cohort effects reported in other studies. The person-time at risk was defined in both Utah and in Norway

from birth to the age of a diagnosis, with censoring at the age of 30 years, death, emigration, end of study or the last known date of residence in Utah.

We present hazard ratios (HR) and 95% CI for the risk of TC among index persons in association with TC in the first-degree relatives separately for fathers, brothers, and all first-degree relatives. The results are presented for the whole population in Utah and in Norway. Analyses were adjusted for number of known male relatives. In addition, we conducted several comparisons between ancestry groups. The comparisons are corrected for multiple testing by the Bonferroni correction (Appendix 1).

The proportional hazards assumption was verified by plotting Schoenfeld residuals. All analyses were performed using SPSS version 25.

Ethics approval and consent to participate: This study was approved by the Institutional Review Boards of the University of Utah and by the Utah Resource for Genetic and Epidemiologic Research (IRB_00090583). In Norway the project was approved by the Regional Committees for Medical and Health Research Ethics, (REK Sør-Øst: 2016/1305). As this is a register-linked study, the approval also covers exemption from informed consent because that would not be feasible to acquire.

Data availability. Data can be made available upon approval from the Institutional Review Boards of the University of Utah, the Utah Resource for Genetic and Epidemiologic Research and the Regional Committees for Medical and Health Research Ethics in Norway.

3. Results

During the 64-year study period, a total of 1,974,287 and 832,836 male births were recorded in Norway and the Utah data resource, respectively (Table 1). Overall 68% of these Utah children had ancestral roots from Scandinavia, of which 20.2% had ancestral roots from Norway specifically. Appendix 2 shows a distribution of ancestry values for children and young adults with ancestry from Scandinavia. During the follow-up period, 2,686 index persons were diagnosed with TC in Norway and 531 in Utah.

3.1 TC incidence

We observed a tendency towards an increase in TC incidence with consecutive birth cohorts in both countries (Figure 1), with the highest incidence rates observed among the most recent birth cohorts analysed in Norway. This trend was statistically significant in both Norway ($p < 0.001$) and in the whole population of Utah ($p < 0.001$). In Norway, incidence rates were ranging from 2.6 among individuals born during 1951-1954 to 10.6 among individuals born during 1980-1984. In the Utah data, the rates were lower, ranging from 2.3 for individuals born during 1951-1954 to 5.1 among individuals born during 1980-1984. Incidence rates of TC among individuals born in the last periods of the study in Utah and Norway showed less increase in incidence compared with earlier cohorts. There was no CI overlap from 1960 and later, indicating that these differences in TC incidence between Norway and Utah were statistically significant after that period.

Individuals with Scandinavian ancestors in Utah also showed a similar trend for increasing incidence of TC ($p=0.003$), while it was not significant for the non-Scandinavian Utah population ($p=0.06$). However, looking at the plot (Figure 1), the trends are very similar and indeed, the incidence rates of TC in Utah did not differ significantly according to presence or absence of Scandinavian ancestry ($p=0.66$).

Non-seminoma TC tumours showed the highest incidence rates in both countries, and statistically significant increasing trends with consecutive birth cohorts, in both Norway ($p < 0.001$) and Utah ($p=0.003$) (Figure 2). Seminomas showed lower incidence rates than non-seminomas, with a statistically significant increased incidence in Norway ($p < 0.001$), but not in Utah ($p=0.085$).

3.2 Family history of TC and TC risk

Overall, we observed an association between a family history of TC in first-degree relatives and risk of TC in index persons in both Norway and Utah (Table 2). Having a brother diagnosed with TC was the strongest risk factor for TC among children born in both Utah (9.9-fold) and in Norway (6-fold). When the Utah results were stratified by Scandinavian ancestry (data not shown) we observed a higher risk for TC when a brother was diagnosed with TC among individuals with Scandinavian ancestry (12.3-fold) than among individuals without Scandinavian ancestry (5.9-fold). However, these two hazard ratios were not significantly different from each other ($p=0.14$).

4. Discussion

To our knowledge, this is the first population-based study to examine differences in incidence and family risk of TC in individuals born in USA with Scandinavian ancestry. We found a significant increase in incidence of TC with increasing year of birth in both populations, but more pronounced in Norway than in Utah. Norwegian males born between 1980 and 1984 had twice the TC incidence found in Utah in the same period.

Our results are concordant with earlier publications of adult TC incidence in Europe,[23,24,25] Canada,[26] and the USA.[27,28] In Denmark men born around 1943 and 1968 showed lower incidence rates than men born just before or just after these years.[30] The authors of the Danish study attributed these lower rates to a rapid change in risk factors for TC among these cohorts. We found that the uninterrupted increase in TC incidence observed in Norway from 1951 to 1979 flattened out for young men born in the subsequent period (1980-1984), probably also explained by change in TC risk factors, yet to be discovered.

Lower incidence rates of TC in Utah than in Norway may be explained by differences in risk factors between the two populations. Epidemiological studies suggest that the incidence of both cryptorchidism and hypospadias has increased in many countries. However, the authors emphasize that registry-based studies do not permit reliable comparisons due to possible under-reporting,[29] making comparison between Utah and Norway difficult. An underlying mechanism of the Testicular Dysgenesis Syndrome could be a shared heritability of these conditions, but there is evidence that a family history of hypospadias or cryptorchidism is not associated with a general increase in the risk of developing TC.[30]

In 1993, Sharpe and Skakkebaek proposed the “oestrogen hypothesis” which postulated that the increase in male reproductive developmental disorders might have occurred because of increased oestrogen exposure of the human foetus or neonate.[31] This hypothesis has been revised in 2001 by introducing the concept of Testicular Dysgenesis Syndrome, a male reproduction-related condition characterized by the presence of symptoms and disorders such as TC, undescended testes, hypospadias and poor semen quality. The rapid increase in the incidence of these disorders in recent years indicates that the causes might be due to environment factors.[32,33] Systematic reviews examining the association between TC and exposure to estrogenic agents in utero include relatively few studies, small study samples and

high study heterogeneity, making it difficult to have conclusive evidence for such association.[34]

Diet might influence circulating hormone levels, by affecting steroid hormone status.[35] Lifestyle factors related to pregnancy, such as maternal smoking and alcohol consumption have also been linked to the risk of TC. Both cryptorchidism and low birth weight have been associated with the risk of TC and maternal smoking. However, more recent studies do not support this hypothesis.[36] Alcohol consumption is associated with lower maternal testosterone levels in pregnancy, and this in turn is associated with higher risk of TC.[37] Some of these risk factors may differ between Utah and Norway.

Mormons have a health code that promotes healthy behaviours such as eating fruits, vegetables and grains and limiting meat, and excludes alcoholic beverages, tobacco, coffee, tea, and other addictive substances. For instance, Utah has the smallest proportion of smokers of any U.S. state (8.9%), while the current smoking prevalence in Norway is 12%.[38,39] Mormon women are more likely to have more pregnancies and less likely to use birth control pills than Norwegian women, which in turn can affect hormone levels. [40,41] Utah has one of the highest fertility rates in the USA, with 2 children for every one mother.[42] In Norway, the fertility rate was 1.56 in 2018 and has remained stable under 2 in the study period.[43] The percentage of pregnancies resulting from some form of fertility treatment is 4 in Utah and 6.6% in Norway.[44,45] Exogenous hormones and endocrine disruptors have also been suggested as potential risk factors because of their capacity to perturb normal hormonal actions, However, there is a striking lack of human data to fill the current knowledge gaps.[46,47]

Several studies conducted among immigrant populations suggest an influence of life-style and environmental factors in the aetiology of TC cancer.[48,49] Both, in Sweden and Denmark, first-generation immigrants from low-risk countries tend to have a lower risk of TC compared with native-born in these countries, whereas the risk in second-generation immigrants tends to be similar to that observed in native-born.

The interaction between environmental and genetic factors might play an important role in the risk of TC.[50] Differences in genetic susceptibility might predispose some individuals to be more or less likely to develop a particular disease following exposure to an environmental factor. We observed a cessation of increase in incidence of TC among birth cohorts in the last

period in both populations. The lack of further increase in the incidence rate might be explained by reaching the population fraction of susceptible males prone to acquire TC, given the interaction between their genetic susceptibility and environmental risk factors.

In our analysis we cannot distinguish between cohort effects and period effects that might influence different cohorts at different ages. By dividing the study population into age groups and investigating incidence rates within these groups we could perform a formal age-period-cohort analysis[51] with the aim of understanding the relation between pure cohort effects and effects of certain time periods (maybe independent of age). This could potentially lead to improved understanding of the role of certain environmental exposures in the development of TC. However, due to a limited number of cases in many age groups, we have not pursued this strategy any further.

Previous studies have reported familial aggregation of TC in agreement with our findings,[52] with higher risk for TC among brothers than sons in both Norway and Utah. Full brothers share 50% of their genes plus common environmental and gestational factors. However, no highly penetrant TC predisposition genes have been identified.[6] An explanation of our finding may be sharing of intrauterine factors among brothers. For instance, levels of pregnancy estradiol, the main pregnancy oestrogen, have been found to be strongly associated in successive pregnancies of the same women.[53] Black men have lower risk of TC.[54] It has been hypothesized that as the black mothers have significantly higher testosterone levels, it may imply a lower risk to those children compared with children of white mothers.[55] However, black or African Americans constitute less than 2% of the Utah population.[56]

Summarizing, the observed increase in TC incidence can be viewed as a consequence of a change in risk factors for TC in both Norway and Utah, probably environmental or lifestyle factors.

4.1 Strengths and limitations

A strength of this study is the availability of family information for a large number of individuals who emigrated from Scandinavia to Utah during the last 150 years. Second, both countries have detailed nationwide cancer registries. Utah's and Norway's cancer registries rank amongst the top regarding data quality and completeness.[23,24] This avoids ascertainment, referral, and recall bias. Third, there is a pronounced difference in the incidence of testicular

cancer between Scandinavia and Utah. This allowed us to conduct a unique comparative study of familial aggregation of cancer. Incidence rates were calculated for individuals born between 1951 and1984, to allow the same risk window (until the age of 30) for each individual to develop TC. Thus, it allows truncation-free analyses within the same birth cohort from 1951 in Norway and from 1966 in Utah.

Some limitations are also noted. The incidence of TC peak at the ages 30-34 years, the study could be more generalizable with a longer follow up period including individuals older than 30 years. Cancer cases occurring before 1966 in Utah and 1953 in Norway are censored; therefore, our analysis was left-truncated starting at 1966 and 1953, respectively. In consequence the incidence rates in the first period might be some lower than the expected rates. Nevertheless, TC incidence peak after puberty and TC in children below the age of 15 is uncommon and comprises only 4% of childhood cancers.[1] Another limitation was our inability to pool data for Norway and Utah, preventing direct testing of differences between the two populations. In Utah we used the last known date of residence to censure individuals; those without information on this and moving from Utah were censored to follow up. However, the percent change in the size of Utah population is less than 2% according to 2010-2016 estimates.[57] The Utah data included only those individuals with genealogy data in the UPDB this may result in a potential for selection bias. However, approximately 84% of children born in Utah in 1950 had information on grandparents.[58] The grade of completeness in later years might be higher due to link of UPDB with several registries and census. The study is based on individuals from two primarily Caucasian populations. It is unclear whether our results can be generalised to non-Caucasian populations. Utah has limited racial and ethnic diversity with non-Hispanic whites comprising nearly 80% of the population. Previous studies have shown that the UPDB population is genetically representative of US white and northern European populations.[59,60] Ethnically, the residents of Norway are predominantly Caucasians. About 14% of the actual population in Norway are immigrants, whereby almost half of them come from other European countries.[61]

Although Norwegians, Swedes and Danes are quite homogeneous populations, it should be noted that the incidence of TC in Denmark and Norway is about twice the incidence rates in Sweden.[30] This could introduce some bias in our study. If we made the comparison between the Utah population (and specifically the population with Scandinavian ancestry) and the

Scandinavian population instead of the Norwegian population, the difference would have been somewhat smaller.

5. Conclusion

We found a clear difference in TC incidence among individuals born in Norway and descendants of Scandinavian people born in Utah. Incidence of TC showed a rapid increase both in Utah and in Norway with consecutive birth cohorts. The increase was highest in Norway. These differences in TC rates point to the possibility of environmental influences and/or lifestyle factors. Elevated HR of TC in first degree relatives indicates a heritable contribution. However, simultaneous familial exposure or shared familial susceptibility to an environmental factor may also lead to familial aggregation of TC.

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Conflict of Interest: The authors declare no conflict of interest.

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Table 1

Table 1. Characteristics of males born in Norway and Utah in the period 1951 to 2015. Cases are men who were diagnosed with testicular cancer before age 30 years in Utah (1966-2015) and in Norway (1953-2015).

	Cases		Non-cases	
	Number	**%**	**Number**	**%**
Children born in Utah	531	0.1	832,305	99.9
Country of origin of ancestors				
Not Scandinavia	186	35	262,739	31.6
Scandinavia	345	65	569,566	68.4
Tumour histology				
Seminoma	153	28.8		
Non-seminoma	349	65.7		
Unclassified	29	5.5		
Mean age at cancer diagnosis (SD)				
All cases	22 (6.0)			
Seminoma	25 (2.5)			
Non-seminoma	21 (6.3)			
Children born in Norway	2,686	0.1	1,971,601	99.9
Tumour histology				
Seminoma	761	28.3		
Non-seminoma	1654	61.6		
Unclassified	271	10.1		
Mean age at cancer diagnosis (SD)				
All cases	24 (4.9)			
Seminoma	26 (3.1)			
Non-seminoma	23 (5.2)			

Abbreviations: SD, standard deviation

Table 2

Table 2. Risk of testicular cancer according to family history of testicular cancer among a cohort of males born in Norway and Utah in the period 1951-2015 and who were diagnosed with testicular cancer before age 30 years in Utah (1966-2015) and in Norway (1953-2015). Adjusted hazard ratios (HR) with 95% confidence interval (CI) are presented separately for the whole population in Utah and for Norway.

	All children born in Utah			All children born in Norway		
Family history of testicular cancer	**Cases**	**HR (95% CI)**	p-value	**Cases**	**HR (95% CI)**	p-value
Father	4	**3.47 (1.30-9.28)**	0.0132	35	**4.41 (3.16-6.16)**	**<0.0001***
Brothers	23	**9.87 (5.68-17.16)**	**<0.0001***	76	**6.02 (4.80-7.55)**	**<0.0001***
All first-degree relatives	25	**6.74 (4.27-10.61)**	**<0.0001***	116	**5.54 (4.60-6.68)**	**<0.0001***

The model was adjusted for number of relatives according to type analysis.
Cases: number of cancer cases with relatives affected.
NC: not calculated
Bolding of HRs shows that 95% CI does not include 1.00.
*P-values < ~0,0004 after Bonferroni test correction are still significant and highlighted in the Table.

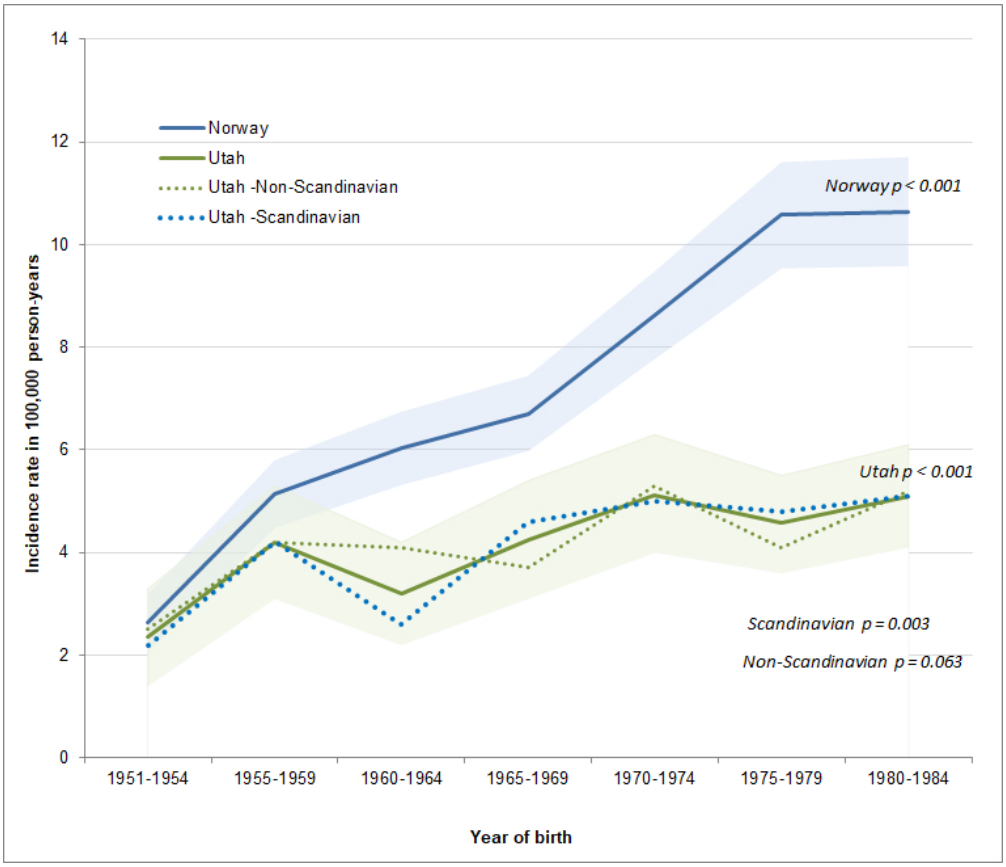
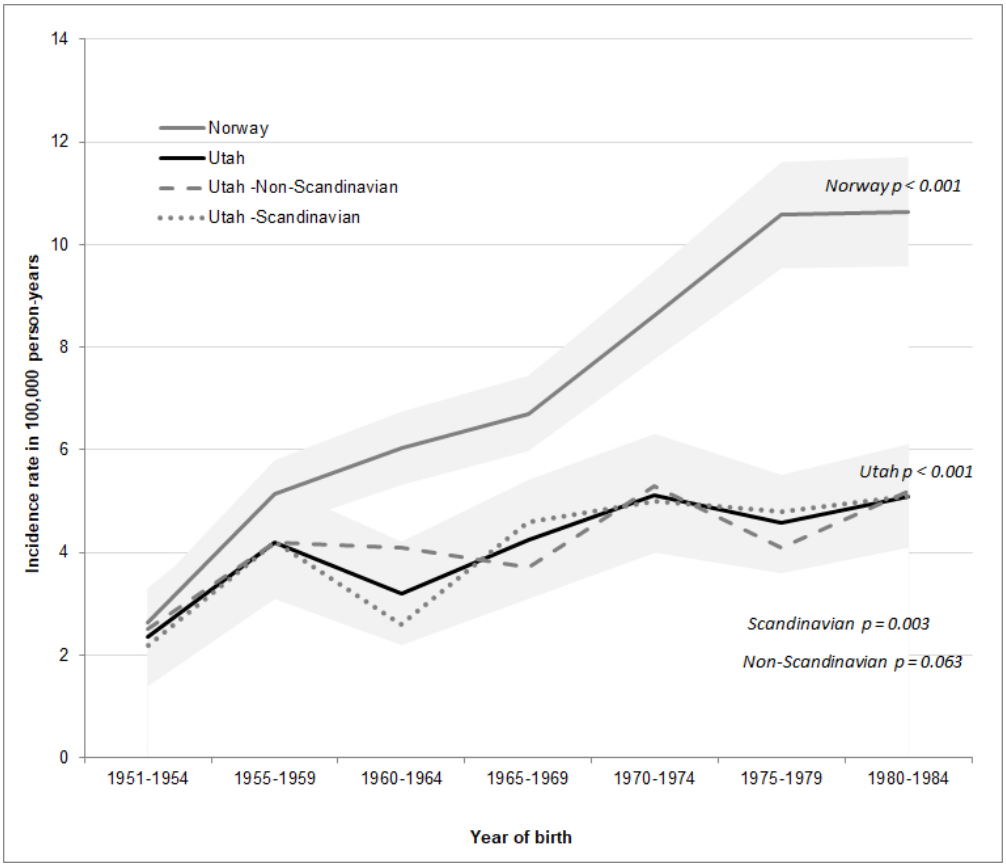


Figure 1. Testicular cancer incidence rates with 95% confidence intervals among males born in Norway and Utah in the period 1951-2015 and who were diagnosed before 30 years with TC in Utah (1966-2015) and in Norway (1953-2015).
In Utah the incidence rates are presented separated with dotted lines for males with and without Scandinavian ancestors. Light blue and green colour represents 95% confidence intervals. P means p values for trend.

202x173mm (96 x 96 DPI)



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In Utah the incidence rates are presented separated with dotted lines for males with and without Scandinavian ancestors. Light grey colour represents 95% confidence intervals. P means p values for trend.

202x173mm (96 x 96 DPI)

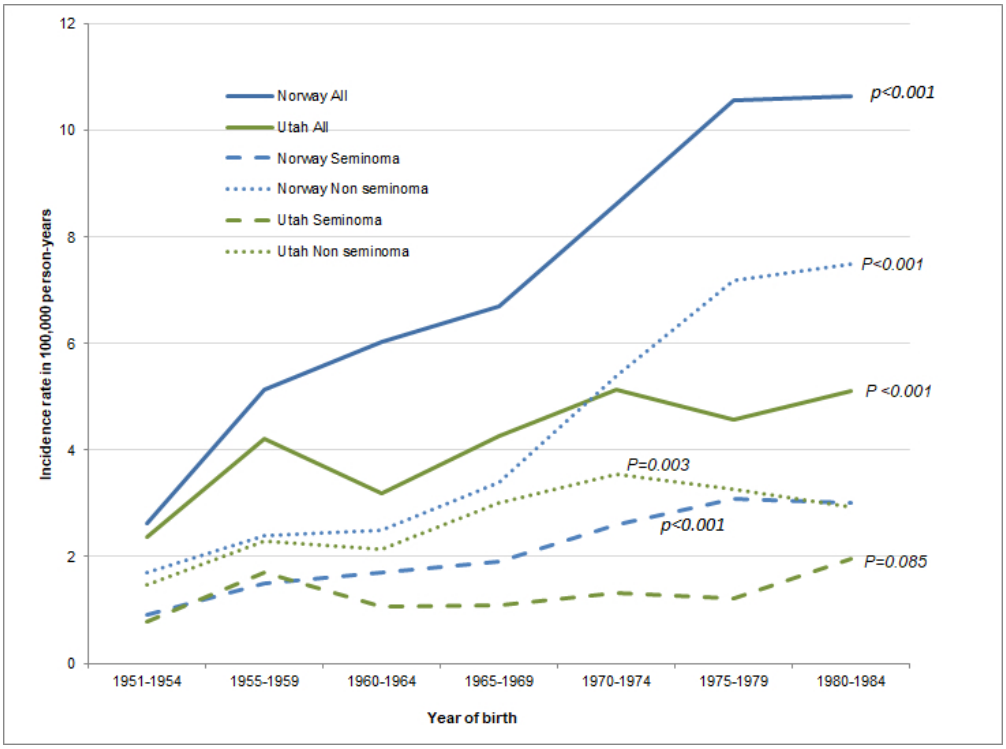
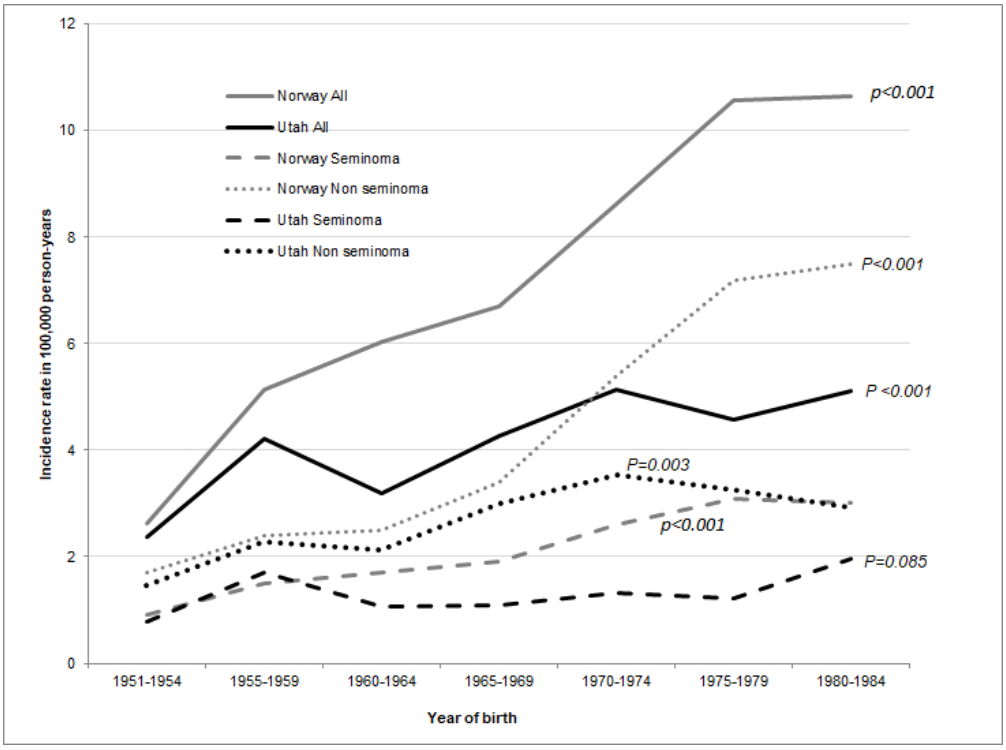


Figure 2. Testicular cancer incidence rates across histological groups among males born in Norway and Utah in the period 1951 to 2015 and who were diagnosed before 30 years with TC in Utah (1966-2015) and in Norway (1953-2015).
P means p values for trend.

193x143mm (96 x 96 DPI)



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