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## Original Paper

# Trends in Incidence of Testicular Cancer in Norway 1955–1992

E. Hoff Wanderås,[1] S. Tretli[1] and S.D. Fosså[2]

[1]The Cancer Registry of Norway, Institute for Epidemiological Cancer Research, Montebello, 0310 Oslo; and [2]The Norwegian Radium Hospital, Montebello, 0310 Oslo, Norway

**The aim of this study was to explore the incidence of testicular cancer (TC) in Norway, and thereby to increase the understanding of aetiological factors. From 1955 to 1992, a total number of 3927 TC cases were recorded in Norway, of which 51% were seminomas, 45% non-seminomas and 4% other and unspecified types. The age-standardised incidence rate increased from 2.7 to 8.5 per 100 000. The age-specific incidence rate increased in all age groups, but was most marked in the younger population. The significance of birth cohort as a risk factor for development of TC was confirmed. The incidence by birth cohorts from 1916 to 1970 showed an increase by later birth cohorts during the whole period, with the exception of a marked fall for the cohort born during the Second World War. The largest increase occurred after the war. We conclude that environmental factors acting very early in life are of significance in the development of TC.**

**Key words: testicular-neoplasms-epidemiology, incidence, Norway, registries, risk factors, aetiology, birth cohort-effect, environment**

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## INTRODUCTION

THE INCIDENCE of testicular cancer (TC) varies widely among the Nordic countries. The age-standardised cumulative incidence rates in 1986 varied between 8.4 per 100 000 person years in Denmark, one of the highest in the world, 6.6 in Norway and 1.8 in Finland (World Standard) [1]. The reasons for this great difference are not clear.

The fact that TC is a cancer of younger age groups, has led to the hypothesis that carcinogenesis starts very early in life, probably as early as in uterine life. Both epidemiological [2–4] and basic medical research [5, 6] have demonstrated that the period of gonadal differentiation in early fetal life is of importance. The only established risk factors so far have been cryptorchidism and Caucasian race. Other possible risk factors under discussion are low birth weight, high age of the mother at the time of the patient's birth, first among siblings, high maternal weight, nausea, hyperemesis and bleeding in pregnancy, high social class and genetic factors apart from race [7]. Møller [8] reported that the incidence was temporarily reduced for the cohort of men born just before and during the Second World War. This underlines the assumption that environmental factors may be of importance.

The aim of this study was to use the high quality data of the Norwegian Cancer Registry to explore the trends of incidence of TC in Norway during a 40 year period, and thereby to increase the understanding of aetiological factors. In particular, the importance of birth cohort as a risk factor was addressed.

Correspondence to E. Hoff Wanderås.
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## PATIENTS AND METHODS

*Patients*

Cancer reporting to the Norwegian Cancer Registry has been compulsory since the registry was established in 1952. All hospitals and histopathological laboratories are independently committed to report all newly diagnosed cases of cancer. The identification of Norwegian inhabitants is simplified through an 11 digit personal identification number which unambiguously identifies each Norwegian inhabitant.

The present study comprises all cases of malignant tumours located in the testicle which were reported to the Cancer Registry between 1955 to 1992, except 54 patients with a primary malignant lymphoma of the testis. Patients with concomitant or subsequent cancer in both testicles were recorded as one case.

Registration is based on the International Classification of Diseases, 7th Revision (ICD-7, 1955). The histological classification and coding was carried out according to the Manual of Tumor Nomenclature and Coding, 1968 (MOTNAC) and Systematized Nomenclature of Pathology, 1965 (SNOP). Ninety-eight per cent of the tumours were histologically verified.

The tumours were grouped as follows: seminomas, non-seminomas and other histological and unspecified types. The extent of the disease was referred to as stages I–III: stage I (no

evidence of metastases), stage II (regional metastases), and stage III (metastases other than regional).

The patients' age at diagnosis and the diagnostic periods were divided into 5 year intervals, except for the latest 3 year diagnostic period from 1990–1992. The age-adjustments were made according to The World Standard Population.

The increase in incidence rate of TC per 5 year age groups was estimated by a loglinear model. The mean incidence of 5 year diagnostic periods from 1958 to 1992 was used as the basis of the estimation of the annual increase. The increase in the 15–19 years age group for seminomas was not possible to calculate due to lack of observations in some cells.

To study the birth cohort effect, an age–period–cohort model was attempted. The population was divided into 5 year age groups (15–19,. . ., 40–44) and 5 year birth cohorts (1916–1920,. . ., 1966–1970) and seven diagnostic periods covering the calendar period 1955–1989. Let $D_{ijk}$ be the number of observed cases in age group $i$, birth cohort $j$ and diagnostic period $k$, and $N_{ijk}$ the number of persons at risk. $D_{ijk}$ is assumed to have Poisson distribution with mean $\exp(x + a_i + b_j + P_k + \log(N_{ijk}))$ where x is the constant term, $a_i$ is the age effect, $b_j$ the birth-cohort effect and $P_k$ the period effect. Estimation and testing were carried out via the GLIM 3.77 statistical programme. An acceptable best fit appraised by the deviance was achieved by including the variables age and birth cohort only. Since diagnostic periods were without importance, but were defined with overlapping periods, a new model defining age and diagnostic periods as clean 5 year groups and overlapping birth cohorts, was attempted. This analysis revealed that a model including age and period of diagnosis only did not achieve an acceptable best fit. Our final model was, therefore, expressed through the mean $\exp(x + a_i + b_j + \log(N_{ijk}))$. The model was also applied in subanalyses regarding histological types.

## RESULTS

From 1955 to 1992, a total number of 3927 testicular cancers were recorded in Norway (Table 1). Of these, 91% occurred in patients between 10 and 59 years of age, 51% were classified as seminomas, 45% as non-seminomas and 4% as other and unspecified types. Only 1% of the tumours occurred in boys under the age of 9 years, and the majority of these were classified as non-seminomas. In the age group 10–34 years, non-seminomas were the most frequent histological type (61%), while seminomas dominated with 71% in the 35–39 year age group. In addition, in the oldest age group (60+) which accounted for 7% of cases, seminomas dominated with 57%.

Other histological and unspecified types occurred most often in the youngest and oldest age groups. Half of the tumours of this type were not histologically classified. In the youngest age group, sarcoma dominated with 5 cases of rhabdomyosarcoma and 2 cases of sarcoma that were not further specified. In the oldest age group, histological examination was not available in 35 cases. Fourteen tumours were of the sarcoma type, eight of carcinoma type, nine were malignant tumour not further specified, and there was one case of a carcinoid tumour.

The age-standardised incidence rate of TC increased from 2.7 per 100 000 person years in 1955–1959 to 6.8 in 1985–1989 and 8.5 in the latest period from 1990–1992 (Figure 1). The increase was found for both seminomas and non-seminomas. During the first half of the investigated period, seminomas were slightly more frequent than non-seminomas. The incidence rates of other and unspecified types have been low and stable.

The age-specific incidence rates of seminomas and non-seminomas are demonstrated for three diagnostic periods in

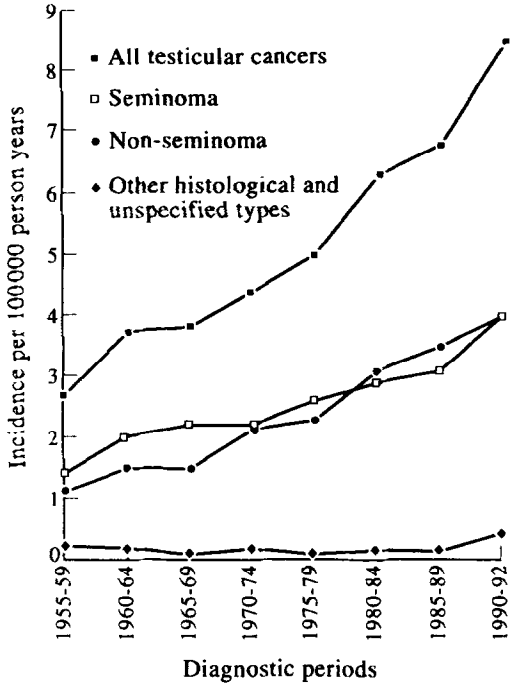


**Figure 1. Age-standardised (World Standard) incidence of testicular cancer in Norway by histological type and diagnostic periods.**

*Table 1. Distribution of testicular cancer in Norway 1955–1992 by histological type and broad age groups in number of cases and per cent*

| Histological type (% distribution of histological types) | Age (years) 0–9 No. | % | 10–34 No. | % | 35–59 No. | % | 60+ No. | % | All ages No. | % |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-seminoma | 40 | 2 | 1253 | 72 | 400 | 23 | 56 | 3 | 1749 | 100 |
| (%) | (75) | | (61) | | (26) | | (20) | | (45) | |
| Seminoma | 1 | <1% | 754 | 38 | 1087 | 54 | 163 | 8 | 2005 | 100 |
| (%) | (2) | | (37) | | (71) | | (57) | | (51) | |
| Other and unspecified types | 12 | 7 | 51 | 29 | 43 | 25 | 67 | 39 | 173 | 100 |
| (%) | (23) | | (2) | | (3) | | (23) | | (4) | |
| Total | 53 | 1 | 2058 | 52 | 1530 | 39 | 286 | 7 | 3927 | 100 |
| (%) | (100) | | (100) | | (100) | | (100) | | (100) | |

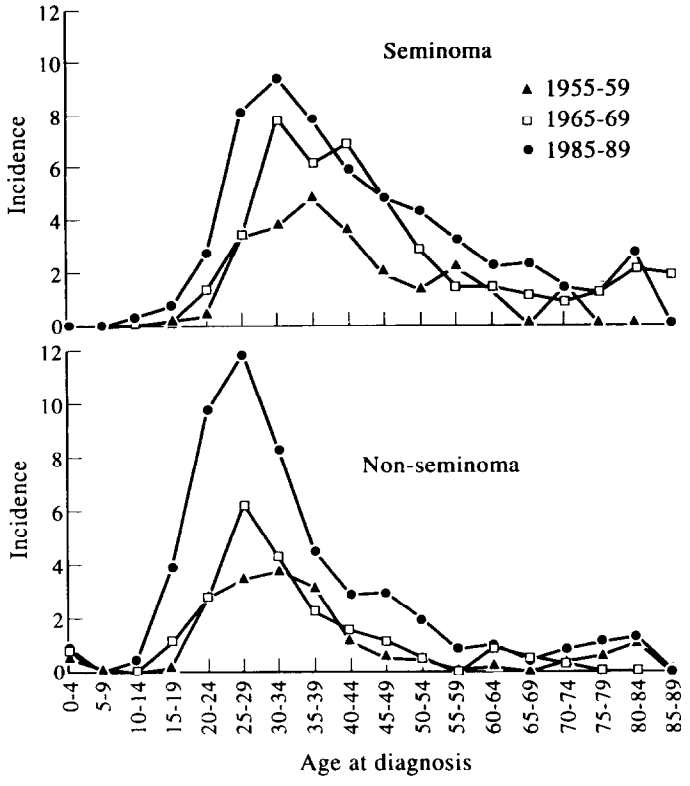


**Figure 2. Age-specific incidence per 100 000 person years of seminomas and non-seminomas in Norway during three diagnostic periods.**

Figure 2. In 1955–1959, the highest incidence rate of seminomas was seen in the age group 35–39 years. In 1985–1989, the highest incidence appeared in the age group 30–34 years. In 1985–1989, patients with seminoma were on average 1.5 years younger and patients with non-seminoma 1.3 years younger at the time of diagnosis compared to patients in 1955–1959. Patients with non-seminoma were on average 8.9 and 8.7 years younger than the patients with seminoma in 1955–1959 and 1985–1989, respectively.

Table 2 shows the annual per cent increase in incidence observed during the period 1955–1992. An increase was seen for all age groups. The highest increase, however, occurred among the youngest men (15–19 years) and the second highest among the oldest men (50–54 years).

Seminoma was most often diagnosed in stage I. This stage is also responsible for the main increase in seminoma incidence rate (data not shown). In stage II, there was a slight increase and in stage III a slight reduction in incidence rate. For non-seminomas, 60% of the patients presented with stage I and 40% with stage II and III at the beginning and at the end of the diagnostic period. In the middle of the period the frequency of stage I and stage II–III was similar. The proportion of stage II increased until early in the 1980s, but decreased thereafter. In the last decade, an increase of stage I was observed.

Figure 3 shows the incidence rates in 5 year birth cohorts from 1916 to 1970 estimated by the described age and birth cohort model. There was an increase in incidence for later birth cohorts up to the birth cohort 1936–1940, for which there is a tendency to level off. A dip appeared for the Second World War cohort (1941–1945), while in the post-war cohorts the incidence rates increased markedly. The calculated incidence rates for the oldest and youngest birth cohorts, however, represent uncertain values.

The age-cohort model was fitted for seminomas and non-seminomas separately using the incidence rates of birth cohort 1916–1920 as reference (Table 3). The relative risks for both seminomas and non-seminomas show patterns similar to the incidence of all testicular cancers combined.

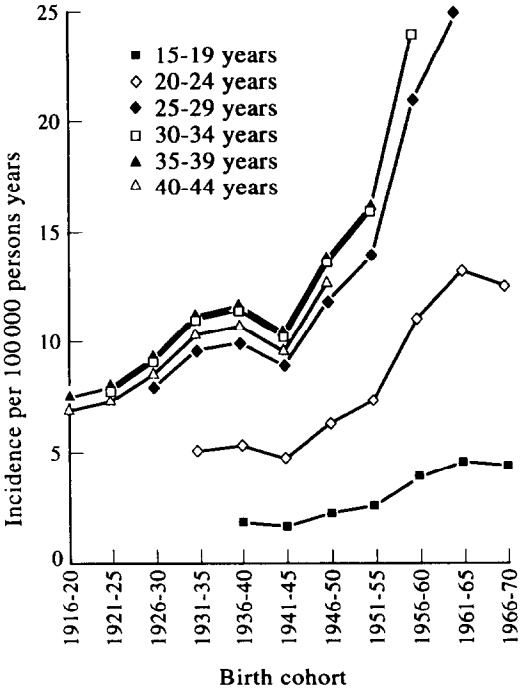


**Figure 3. Estimated incidence of testicular cancer by age at diagnosis and birth cohorts.**

*Table 2. Annual increase in incidence of testicular cancer during the period* 1958–1992 *by histological types and age at diagnosis*

| | Age (years) at diagnosis | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 15–19 | 20–24 | 25–29 | 30–34 | 35–39 | 40–44 | 45–49 | 50–54 |
| All, % (95% CI) | 6.5 (4.8, 8.0) | 4.8 (3.5, 6.0) | 3.0 (1.0, 5.0) | 2.5 (0.2, 4.8) | 2.0 (1.4, 2.6) | 1.7 (−0.4, 3.8) | 2.9 (1.1, 4.8) | 3.9 (1.9, 5.9) |
| Seminoma, % (95% CI) | — | 7.2 (1.8, 3.0) | 3.4 (0.2, 6.8) | 2.1 (−1.3, 5.6) | 1.8 (1.1, 2.4) | 0.8 (−1.9, 3.7) | 2.9 (0.1, 5.8) | 3.5 (1.2, 5.9) |
| Non-seminoma, % (95% CI) | 6.7 (4.8, 8.5) | 4.6 (2.8, 6.5) | 2.8 (1.5, 4.5) | 2.9 (0.9, 4.8) | 2.5 (1.7, 3.4) | 4.7 (1.5, 7.9) | 3.1 (−1.3, 7.7) | 4.6 (1.0, 8.5) |

CI, confidence interval.

*Table 3. Relative risk and 95% confidence interval of seminomas and non-seminomas in 5 year birth cohorts from 1916 to 1970*

| | 1916–1920* | 1921–1925 | 1926–1930 | 1931–1935 | 1936–1940 | 1941–1945 | 1946–1950 | 1951–1955 | 1956–1960 | 1961–1965 | 1966–1970 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Seminoma | 1.00 | 0.97 | 1.29 | 1.42 | 1.42 | 1.25 | 1.58 | 2.06 | 2.80 | 3.15 | 3.51 |
| (95% CI) | | (0.62, 1.32) | (0.96, 1.61) | (1.09, 1.75) | (1.09, 1.74) | (0.93, 1.57) | (1.26, 1.9) | (1.73, 2.4) | (2.44, 3.16) | (2.71, 3.59) | (2.8, 4.22) |
| Non-seminoma | 1.00 | 1.30 | 1.18 | 1.70 | 1.85 | 1.65 | 2.29 | 2.46 | 4.00 | 4.82 | 4.41 |
| (95% CI) | | (0.73, 1.86) | (0.62, 1.73) | (1.16, 2.23) | (1.32, 2.37) | (1.13, 2.16) | (1.78, 2.81) | (1.93, 2.98) | (3.48, 4.53) | (4.28, 5.35) | (3.83, 4.99) |

CI, confidence interval; * Reference category.

## DISCUSSION

The incidence of TC has been increasing in several industrialised countries during this century, especially in Northern Europe and in North America [9, 10]. The highest incidence rates have been observed in Denmark, Norway and Germany [10].

The findings in our study on TC in Norway are much like those from a previous study from the Danish population [8]: a similar distribution of the different histological types within and between age groups, as shown in Table 1, indicates a similar pattern of manifestation of TC and similar practice of histological classification in the two countries. The incidence, however, remains somewhat lower in Norway than in Denmark.

*Histology*

At the Norwegian Cancer Registry before 1983, tumours with both seminomatous and non-seminomatous elements were classified as seminomas if the seminomatous component dominated. This coding was changed in 1983 allowing strict discrimination between pure seminomas and non-seminomas with or without seminomatous structures. For the present study, no reclassification was performed for the period before 1983, but the misclassification was probably of limited significance.

The main reason for the reduction in the average age at diagnosis for both seminoma and non-seminoma patients is that the largest increase in incidence rate has occurred in the younger age groups. A gradual improvement in patient's and doctor's delay represents another explanation. The more aggressive nature of non-seminomas compared to seminomas is indicated through the much lower average age at diagnosis.

*The stage of the TC at time of diagnosis*

The stage allocation of a patient's cancer disease depends on the available diagnostic methods as well as the degree of delay of diagnosis and the aggressiveness of the malignant tumour itself.

During the study period, considerable optimisation of diagnostic procedures has taken place for patients with TC. These circumstances have especially influenced stage allocation of the more aggressive non-seminomas, and it is thus difficult to give an exact statement on the true changes in this histological subgroup during the investigation period. Nevertheless, changes, if any, have probably been small for non-seminomas.

There is good reason to believe that the diagnostic delay has gradually been reduced in Norwegian patients with TC, similarly for seminoma and non-seminoma patients. A short delay favours the patient's presentation with stage I disease, in particular the seminoma patients. In patients with the biologically more aggressive non-seminoma, metastases seem to occur more independently from the duration of the delay.

*The birth cohort effect*

A very interesting finding in our analysis is the relationship between birth cohort and TC, in particular the fall in incidence rate for the cohort born during the last World War. The latter observation was surprising since it has been claimed that no such effect exists in Norway [8].

We notice that there is a weak indication of a levelling-off in incidence rate for the youngest cohort born in 1966–1970. The same observation has been made in Denmark [11]. This may be a random phenomenon, but hopefully it is not.

The most interesting observation, however, is a lower incidence rate than expected for those born during the Second World War, and to a lesser extent during the 5 year period before the war. This is in accordance with the results from the Danish study [8], and strengthens the assumption that this observation is real. The observed levelling-off for the cohorts born just before the Second World War indicates that any protective environmental influence occurring during the war time might not only have been effective during fetal life in those individuals born during the war, but may also have reduced the risk of subsequent TC in early childhood in those boys born in the late 1930s. Another possibility is that the environmental factors we are looking for started to change before the war.

The marked fall in incidence rate observed during the war poses many questions and new approaches to the aetiology of TC. Firstly, it strongly indicates that environmental factors are of importance. While the Norwegians were occupied by the German military forces from 1940–1945, the life-style changed in several ways: import and export of goods were markedly reduced [12]. These circumstances led to changes in daily diet, agriculture and industry, reduced use of polluting vehicles and increased physical activity. A marked failure in the import of food together with changes in agriculture, led to a reduction in calorie intake and fat consumption, and an increase in the consumption of vegetables and dietary fibre for most Norwegians [13, 14].

A low fat, high fibre diet reduces the concentration of total and free oestradiol in blood in man significantly, but affects the androgens to a lesser degree [15, 16]. A correct balance of the sex hormones, especially testosterone and oestradiol, is important for normal differentiation of the gonadal tissue in early fetal life, but it may also cause an increased risk of developing *in situ* carcinoma of the testicle [5].

In case–control studies, no connection between smoking and TC has been found [17, 18]. A possible relationship between smoking habits in pregnancy and TC, however, has not been well studied. From 1920 to 1970, the frequency of smokers among fertile women in Norway has increased [19]. The steepest increase has occurred in the second half of the period, therefore, accompanying the increase in incidence of TC related to the birth cohorts.

During the 1930s, a period with severe economical problems in Norway and high unemployment, the number of births decreased [12]. However, those who married during these years,

conceived at an older age [20]. If high age of the mother was an important risk factor, it should have led to an increase in the incidence of TC during the Second World War, which is the opposite of what we have observed.

Being the first among siblings has been shown to be a possible risk factor for development of TC in epidemiological studies [4]. Other studies have demonstrated higher maternal levels of free oestradiol in the first compared to the second pregnancy [21, 22]. From 1946 to 1970, the annual number of births in Norway as well as the percentage of first born babies have remained almost constant [23]. The possible risk factor of being first among siblings, has, therefore, probably not contributed to the marked increase in incidence of TC among those men born after the war.

Very interesting, but difficult in the search for aetiological factors in the development of TC, is the aspect of contamination of the environment. During the last few years, interest has been focused on the oestrogenic activity of many chemicals in our environment and their possible deleterious effect on reproductive function in animals and man [24].

During the Second World War, contamination was reduced in Norway because of a lower industrial activity, a reduced import and use of commercial fertilisers, feeding stuff and pesticides in agriculture and a reduction in the use of motorised vehicles due to lack of gasoline [12]. In post-war time, however, the use of chemicals both in agriculture and in industry resumed in an uncontrolled way.

If the hypothesis of a causal relationship between oestrogens during early pregnancy and the carcinogenesis of testicular cancer are justified, it would be of great interest to determine how much pregnant women are and have been exposed to environmental oestrogen-like substances. The diversity in chemical structure of substances with oestrogenic activity [25] makes the solution to this problem even more difficult and challenging.


1. Parkin DM, Muir CS, Whelan SL, Gao, Y-T, Ferlay J, Powell J. *Cancer Incidence in Five Continents*. VI. IARC Scientific publications, 1992, **120**, 972–973.
2. Schottenfeld D, Warshauer ME, Sherlock S, Zauber AG, Leder M, Payne R. The epidemiology of testicular cancer in young adults. *Am J Epidemiol* 1980, **112**, 232–246.
3. Giwercman A, Grindsted J, Hansen B, Jensen OM, Skakkebaek NE. Testicular cancer risk in boys with maldescended testis. A cohort study. *J Urol* 1987, **138**, 1214–1216.
4. Prener, A, Chung-cheng H, Engholm G, Trichopoulos D, Jensen OM. Birth order and risk of testicular cancer. *Cancer Causes Control* 1992, **3**, 265–272.
5. Rajpert-De-Meyts, Skakkebaek NE. The possible role of sex hormones in the development of testicular cancer. *Eur Urol* 1993, **23**, 54–61 (Review).
6. Walker AH, Bernstein L, Warren DW, Warner NE, Zheng X, Henderson BE. The effect of *in utero* ethinyl oestradiol exposure on the risk of cryptorchid testis and testicular teratoma in mice. *Br J Cancer* 1990, **62**, 599–622.
7. Forman D, Gallagher R, Møller H, Swerdlow TJ. Aetiology and epidemiology of testicular cancer: report of the Consensus Group. *EORTC Genitourinary Group Monograph 7: Prostate Cancer and Testicular Cancer* 1990, 245–253 (Review).
8. Møller H. Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology. *Eur Urol* 1993, **23**, 8–15.
9. Doll R, Payne P, Waterhouse J. *Cancer Incidence in Five Continents*. Berlin, UICC, Springer, 1966.
10. Adami HO, Bergström R, Möhner M, *et al.* Testicular cancer in nine northern European countries. *Int J Cancer* 1994, **59**, 33–38.
11. Bergström R, Adami HO, Möhner M, *et al.* Increase in testicular cancer incidence in six European countries; a birth cohort phenomenon (*submitted*).
12. Central Bureau of Statistics. *Statistical Survey 1948*. Oslo, 1949.
13. Strøm A. Examination into the diet of Norwegian families during the war-years 1942–1945. *Acta Med Scand* 1948, **214**, 3–47 (suppl).
14. Hansen OG. Food conditions in Norway during the War, 1939–1945. *Proc Nutr Soc* 1947, **5**, 263–270.
15. Barbosa JC, Schultz TD, Filley SJ, Nieman DC. The relationship among adiposity, diet, and hormone concentrations in vegetarian and nonvegetarian postmenopausal women. *Am J Clin Nutr* 1990, **51**, 798–803.
16. Bennet FC, Ingram DM. Diet and female sex hormone concentrations: an intervention study for the type of fat consumed. *Am J Nutr* 1990, **52**, 808–812.
17. Brown LM, Pottern LM, Hoover R. Testicular cancer in young men: the search for causes of the epidemic increase in the United States. *J Epidemiol Community Health* 1987, **41**, 349–354.
18. Coldman AJ, Elwood JM, Gallagher RP. Sports activities and risk of testicular cancer. *Br J Cancer* 1982, **46**, 749–756.
19. Rønneberg A, Hafstad A, Lund KE. Røykevaner siden 1910 blant norske menn og kvinner født etter 1890. *Tidsskr Nor Laegeforen* 1994, **114**, 1623–1626.
20. Central Bureau of Statistics. *Barnetall i ekteskap. Rapporter 88/21*. Oslo, Kongsvinger, 1988.
21. Bernstein L, Depue RH, Ross RK, Judd HL, Pike MC, Henderson BE. Higher maternal levels of free estradiol in first compared to second pregnancy: early gestational differences. *J Natl Cancer Inst* 1986, **76**, 1035–1039.
22. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal age, parity and pregnancy estrogens. *Cancer Causes Control* 1990, **1**, 119–124.
23. Central Bureau of Statistics. *Historical Statistics 1978*. Oslo-Norway, p52, tbl.17.
24. Roychowdhury M. Reproductive hazards in the work environment. *Professional Safety* 1990, **35**, 17–22.
25. McLachlan JA, Korach KS, Newbold RR, Degen GH. Diethylstilboestrol and other estrogens in the environment. *Fundam Appl Toxicol* 1984, **4**, 686–691.


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