Eur J Cancer Clin Oncol, Vol. 23, No. 6, pp. 827–830, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00
© 1987 Pergamon Journals Ltd.

Changes in Testicular Cancer in Scotland

PETER BOYLE,* STANLEY B. KAYE† and A. GERARD ROBERTSON‡

*Unit of Analytical Epidemiology, International Agency for Research on Cancer, 150 cours Albert Thomas 69372 Lyon, France, †University of Glasgow, Glasgow, U.K. and ‡Institute of Radiotherapeutics and Oncology, Western Infirmary, Glasgow, U.K.

Abstract—*There are two purposes to this paper. Firstly to describe the temporal pattern of germ-cell testicular cancers in Scotland, both as a single entity and as the histological sub-types (pure) seminoma and teratoma. Incidence rates rose by over* 50% *between* 1959 *and* 1984, *with the rates of seminoma increasing only marginally and the majority of the overall increase accounted for by the substantial increase observed among the sub-type teratoma.*

Secondly, to investigate the impact of new therapies on the mortality rate from germ-cell testicular cancer in Scotland in the light of improvements in survival rate reported during the last 25 *years from clinical trials and clinical series. Noticeable changes have occurred in the temporal pattern of mortality which cannot be explained by changes in incidence. The ever-widening gap between the increasing incidence rate and the declining mortality rate, particularly apparent in the high-risk age group* 15–44, *indicates an improving prognosis for patients with this malignancy in Scotland.*

INTRODUCTION

ALTHOUGH an uncommon tumour, several studies have shown that the incidence of germ-cell testicular cancer is increasing, particularly in the young (under 45), with the incidence rates in Scotland currently in the upper 50% of incidence rates reported worldwide [1]. The aetiology of testicular cancer is largely unknown and there is little explanation for the apparent downward shift in the peak of the age incidence curve [2, 3]. Previous studies which have examined incidence and mortality of germ-cell testicular cancer have failed to examine time trends in the various histological sub-types.

The study reported here has two purposes. Firstly, to examine the changing temporal pattern of germ-cell testicular cancer in Scotland via routinely collected data over the period 1959–1985, paying particular attention to patients with histologically documented teratoma and pure seminoma, both groups being considered separately. This division was chosen because the biological behaviour of tumours with any proportion of teratoma may well differ significantly from tumours which are pure seminoma.

The second purpose was to examine the impact of improved therapy on the mortality from germ-cell testicular cancer in Scotland. In the past 25 years, the management of germ-cell testicular cancer has improved considerably, particularly in patients with disseminated cancer [4]. These reports of improvement in survival, while dramatic, were based on clinical trials and clinical series with the usual problems of being observations on highly selected patients, or groups of patients, in selected hospitals [5]. It is more reliable, when assessing the impact of improvements in therapy on the general population of patients, to examine temporal trends in mortality and to compare these trends in incidence, where the latter are available.

Incidence and mortality data exist for Scotland (population 5 million), one of only a small number of countries where this is the case.

MATERIALS AND METHODS

Mortality data were abstracted from the annual reports of the Registrar General for Scotland [6] for the years 1959–1984 (inclusive). Data were published as numbers of deaths per 5 year age grouping, the population of Scotland being published in similar format in the same volumes.

Incidence data were collected by the Scottish National Cancer Registration Scheme via five, population-based, regional registries in Glasgow, Edinburgh, Dundee, Aberdeen and Inverness. This scheme was introduced in July 1958 and data are considered to be reasonably complete from 1960 onwards.

Information on histological tumour type was collected by the Scheme and has been classified by the International Classification for Diseases for

Accepted 16 December 1986.

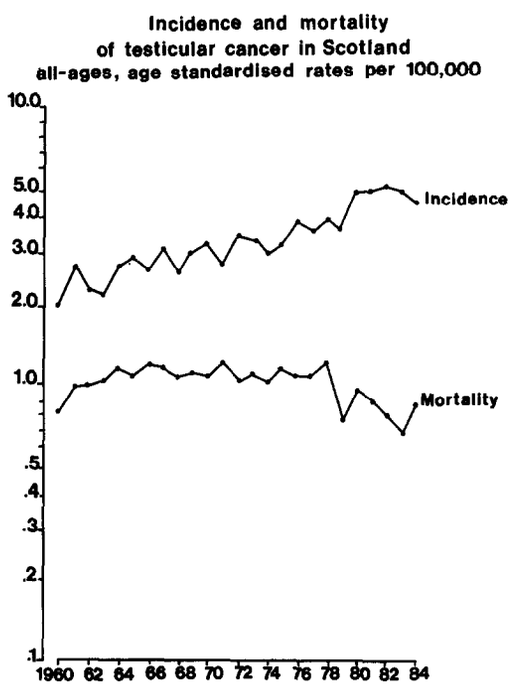

Fig. 1. *All ages, age-standardized incidence and mortality rates per* 100,000 *in Scotland,* 1960–1984.

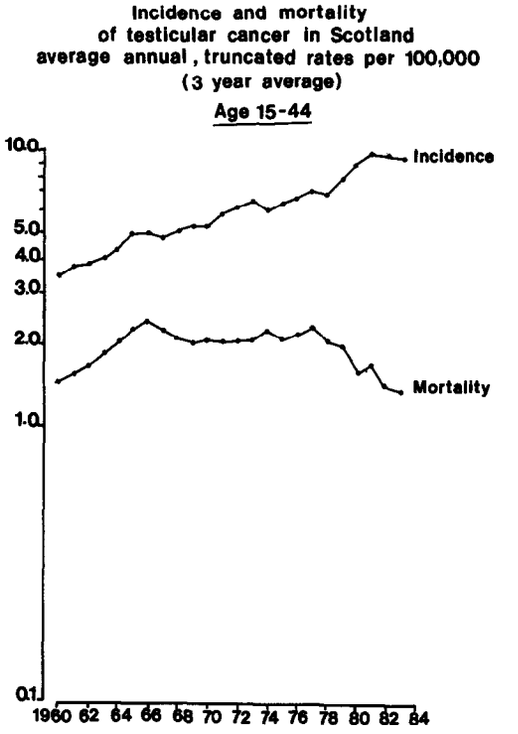

Fig. 2. *Truncated* (15–44), *age-standardized moving average incidence and mortality rates per* 100,000 *in Scotland,* 1960–1984.

Oncology (ICD-O) [7]. Tumours have been classified into two broad sub-types: (pure) seminoma or teratoma. Tumours with a mixed histological pattern, thought to comprise 14% of testicular cancer [8], have been considered as *teratoma* since it is the presence of histologically confirmed teratoma in any proportion in a specimen which determines how such patients will be treated.

In all data presented, rates have been age-standardized with the World Standard Population employed throughout [9]. Because of the relative infrequency of this cancer, a moving-average age-standardized rate has sometimes been calculated when investigating truncated rates. This was done by aggregating the age-specific data for the years 1959, 1960 and 1961 and then age-standardizing. The resultant average annual age-standardized rate per 100,000 person-years was taken as the rate for 1960. Data for 1962 were then included and 1959 omitted to produce a rate for 1961 and so on.

RESULTS

The incidence of germ-cell testicular cancers rose in all ages between 1959 and 1984 at a fairly constant rate. Mortality, on the other hand, rose until 1965 and declined very slowly until 1977 when the rate of decline increased (Fig. 1). This pattern was more clearly portrayed among young men (aged 15–44) where the highest rate of this disease is present (Fig. 2).

Among both age groups considered (15–44 and 45+), the incidence of seminoma rose very slightly during the period of observation whereas the incidence rates of teratoma increased more rapidly with the difference between the two incidence rates gradually decreasing (Figs. 3 and 4). The pattern

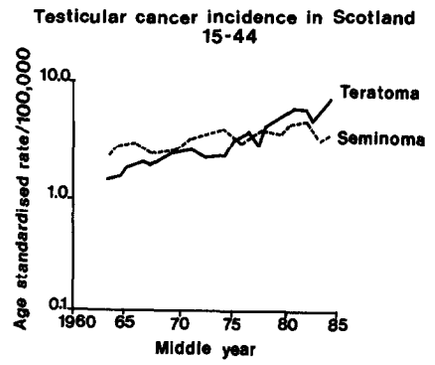

Fig. 3. *Truncated* (15–44) *age-standardized incidence rates per* 100,000 *of (pure) seminoma and teratoma in Scotland,* 1963–1984.

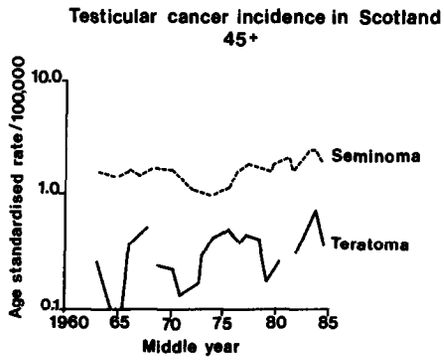

Fig. 4. *Truncated* (45+) *age-standardized incidence rates per* 100,000 *of (pure) seminoma and teratoma in Scotland,* 1963–1984.

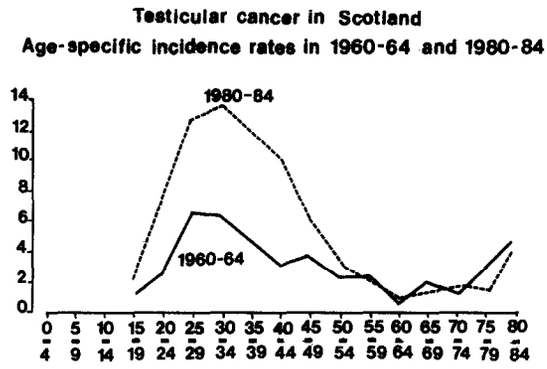

Fig. 5. Average, annual, age-specific incidence rates per 100,000 *of testicular cancer in Scotland*: 1960–1964 *and* 1980–1984.

was more pronounced in the younger group (Fig. 3) of men where the incidence of teratoma had by the end of the period of observation overtaken the incidence of seminoma. No such pattern was observed as clearly among older men (Fig. 4) although there did appear to be an increase in teratoma latterly.

The age-incidence curve changed noticeably between the periods 1960–1964 and 1980–1984. Although rates in older men (over 55) changed very little, there was a large increase in the age-specific rates among younger persons (Fig. 5). Much of this is due to the increases observed in the incidence rates of teratoma (Fig. 3).

DISCUSSION

The results reported here confirm conclusions reached in other studies in two respects. Firstly, there has been approximately a 50% increase in the incidence of testicular germ-cell cancers and previous experience indicates that this is unlikely to be due to an improved rate of diagnosis or registration. Secondly, the peak age has clearly fallen and this disease is now increasingly predominantly a disease of young men.

In addition, this study indicates that these two trends specifically relate to the histological subtype teratoma. Neither the overall incidence, nor the peak age, of pure seminoma has altered significantly over the last two decades. These results would suggest that if a change in aetiological factors has taken place it has resulted in the malignancy manifesting itself more frequently at an earlier age in the form of teratoma.

Several pathological studies have now been performed to support the hypothesis that germ cells within the testis are capable, following malignant transformation, of expressing a range of features dependent on their "age" [10, 11]. In young patients, germ cells retain totipotentiality, i.e. may develop into a varied mixture of embryonal carcinoma, teratoma and choriocarcinoma, all of which are classified together as malignant *teratoma*. With advancing age, it appears that germ cells lose this totipotentiality and upon malignant change will develop into the more uniform histological pattern of *seminoma*.

The nature of the stimulus which results in the development of maligant testicular germ-cell tumours remains to be clarified. The presence of an undescended testis is known to predispose to malignant change and the risk of this cancer may be between 20 and 40 times higher in patients with cryptorchidism as suggested by clinical studies. However, the epidemiological literature places this risk between 2.5 and 8.8 and approximately 10% of testicular cancers occur in patients with cryptorchidism [12, 13]. There may be a genetic component to testicular cancer, which has been reported in identical twin brothers [14], non-twin brothers [15] and fathers and sons [16]. Rates of testicular cancer have generally been shown to be higher in the upper social classes, with the ratio of risk in the highest class as much as 2.5 times that of the lowest class [13]. Most recently, testicular seminoma has been shown to have an increased risk for people engaged in sports activities such as cycling and horse-riding [17].

Whatever the precise nature of the risk factor(s), this examination of Scottish data suggests that patients with testicular germ-cells susceptible to a malignant change are now being exposed to that risk at a considerably earlier age than previously.

In the absence of knowledge of the cause of the overwhelming majority of testicular germ-cell tumours, prospects for prevention are poor. The best hope for a reduction in levels of mortality from testicular cancer lies in improvements in therapy. During the past 25 years, two major advances could be identified in the management of patients with disseminated testicular cancer. In 1960, Li and his co-workers using chemotherapy comprising chlorambucil, methotrexate and actinomycin-D demonstrated that complete remission was obtained in 14% of 72 patients with metastatic disease, although long term control was obtained in only 8% [18].

Subsequently it became apparent that response rates could be increased by the use of vinblastine and bleomycin [19] and when *cis*-platinum was added to that combination results again improved significantly. Thus, in 1977 Einhorn and Donohue reported a 74% complete remission rate among 50 patients receiving platinum, vinblastine and bleomycin for disseminated testicular cancer [20] and it has become clear since then that the majority (60%) have achieved long-term control and almost certainly cure of the disease [4].

As the results obtained in these studies became widely known, the use of chemotherapy for patients with advanced testicular cancer increased and the

impact which this has made on national mortality data for Scotland is clearly shown in Figs. 1, 2 and 3. In the mid 1960s and late 1970s noticeable changes occurred in the temporal pattern of mortality which could not be explained by decreases in incidence. The gap between incidence and mortality has grown since 1965 and continues to do so.

This study has clearly demonstrated that mortality patterns have been changing in a way which is unrelated to changes in incidence, and are quite likely to be the net results of the introduction of improved therapy. It would appear that there are three possible ways, apart from prevention, in which prospects for a further reduction in mortality lie. These are:

(a) earlier diagnosis, since a delay has clearly been shown to have an impact on clinical stage at presentation and ultimate prognosis [21];
(b) improvements in chemotherapy; particularly for patients with far-advanced disease, with the introduction of new drugs such as VP-16 [22, 23]; and
(c) an increased rate of referral for all patients with testicular germ-cell tumours to specialist treatment centres.

Acknowledgements—The authors are grateful to Dr. I.W. Kemp and Mr. P. Trotter of the Information Sevices Division of the Common Services Agency of the Scottish Health Service who supplied incidence data and to Dr. M.A. Heasman for his comments on the manuscript.

REFERENCES

1. Waterhouse JAH, Muir CS, Shanmugaratnam K, Powell J, eds. *Cancer Incidence in Five Continents*. IARC Scientific Publications No. 42, Lyon, IARC, 1982, Vol. IV.
2. Clemmesen J. *Statistical Studies in Malignant Neoplasms. III. Testis Cancer. Acta Path Micro Scand (Suppl.* 209). Copenhagen, Munksgaard, 1969.
3. Davies JM. Testicular cancer in England and Wales: some epidemiological aspects. *Lancet* 1981, **i**, 928–932.
4. Einhorn LH. Testicular cancer as a model for a curable neoplasm. *Cancer Res* 1980, **41**, 3275–3280.
5. Enstrom JE, Austin DF. Interpreting cancer survival rates. *Science* 1977, **195**, 847–851.
6. Registrar General for Scotland. *Annual Report*, 1985. Edinburgh, Her Majesty's Stationery Office, 1986.
7. World Health Organization. *ICD-O International Classification of Diseases for Oncology*, 1st Edn. WHO, Geneva, 1976.
8. Lennox B. Male reproductive system. In: Anderson JR, ed. *Muir's Textbook of Pathology*, 11th Edn. London, Arnold, 1980, 986–1104.
9. Doll R, Smith PG. Age standardised incidence rates. In: Waterhouse JAH *et al.*, eds. *Cancer Incidence in Five Continents*, Vol. IV. Lyon, IARC, 1982.
10. Pugh RCB. Testicular tumours: introduction. In: Pugh RCB, ed. *Pathology of the Testis*. Oxford, Blackwell, 1976.
11. Brawn PN. The origin of germ cell tumours of the testis. *Cancer* 1983, **51**, 1610–1614.
12. Henderson BE, Benton B, Jing J *et al.* Risk factors for cancer of the testis in young men. *Int J Cancer* 1979, **23**, 598–602.
13. Shottenfeld D, Warshauer ME. Testis. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention*. Philadelphia, Saunders, 1982, 947–957.
14. Vallani U. Tumore concordante del testicolo in una coppia di gemelli morozigoit. *Acta Genet Med Gemellol* 1967, **16**, 172.
15. Kademian MT, Caldwell WL. Testicular seminomas: a case report of two brothers with seminoma and a review of the literature of testicular malignancies occurring in closely related family members. *J Urol* 1976, **116**, 380–381.
16. Raghavan D, Jelihovsky T, Fox RM. Father–son testicular malignancy: does genetic anticipation occur? *Cancer* 1980, **45**, 1005–1009.
17. Coldman AJ, Elwood JM, Gallagher R. Sports activities and risk of testicular cancer. *Br J Cancer* 1982, **46**, 749–756.
18. Li MC, Whitmore WF, Golbey R, Grabstald H. Effect of combined drug therapy on metastatic cancer of the testis. *JAMA* 1960, **174**, 1291–1299.
19. Samuels ML, Holoye PM, Johnson DE. Bleomycin combination chemotherapy in the management of testicular neoplasia. *Cancer* 1975, **36**, 318–326.
20. Einhorn LJ, Donohue J. *cis*-Diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med* 1977, **87**, 293–298.
21. Bosl GJ, Vogelzang NJ, Goldman A *et al.* Impact of delay in diagnosis on clinical stage of testicular cancer. *Lancet* 1981, **ii**, 970–973.
22. Fitzharris BM, Kaye SB, Saverymuttu S *et al.* Vp-16-213 as a single agent in advanced testicular tumours. *Eur J Cancer* 1980, **16**, 1193–1197.
23. Newlands ES, Begent RHJ, Rustin GJS, Parker D, Bagshawe KD. Further advances in the management of malignant teratomas of the testis and other sites. *Lancet* 1983, **i**, 948–951.