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Acknowledgments—The authors thank Christine Boudjeda for performing the immunohistochemistry assay, Joelle Fournier and Peggy Jeanne for their excellent technical assistance and Dr Julie Kerr-Conte for the English revision of the manuscript. Supported by grants from the Ligue Nationale Contre le Cancer (Paris) and its Comité du Nord (Lille) and Comité du Pas-de-Calais (Arras).

Pergamon

European Journal of Cancer Vol. 31A, No. 1, pp. 55–58, 1995

0959–8049/95 $9.50+0.00

0959-8049(94)00379-3

A Recent Increase in the Incidence of Prostatic Carcinoma in a French Population: Role of Ultrasonography and Prostatic Specific Antigen

F. Ménégoz, M.Colonna, C. Exbrayat, M. Mousseau, H. Orfeuvre and R. Schaerer

Between 1979 and 1990, the incidence rate (World Standard) for cancer of the prostate in the region of Isère (France) increased from 22.1 to 45.0 cases per 100 000 men, although there was no concurrent increase in mortality (16.0 to 17.6 cases per 100 000 men). This represents a mean increase per year of 6.3% for incidence, compared with 1.3% (NS) for mortality. Incidence of cases with metastases at diagnosis also remained stable with time. In this area, Prostatic Specific Antigen assays began in 1987, and rectal ultrasonography was implemented in 1984, but activity peaked only in 1988. Thus, during 1986–1988, there was both an implementation of new diagnostic procedures and an increase in the incidence of prostatic carcinoma, which suggests that the latter was the result of increased detection of small latent carcinomas. This has implications for public health since apart from increasing costs, it might unduly disturb the life of otherwise healthy people.

Key words: prostatic cancer, epidemiology, incidence, mortality, cancer registry, diagnostic procedures, localised cancer, metastatic cancer, cost, public health

Eur J Cancer, Vol. 31A, No. 1, pp. 55–58, 1995

INTRODUCTION

INCIDENCE AND mortality rates from prostate cancer are highly variable among different countries and ethnic groups [1–3]. More recently, a marked increase in incidence has been described, raising the question of whether the risk, diagnostic measures (or reporting attitudes), or both, have changed [4–6]. Lu-Yao and Greenberg [7] believe that, in the U.S.A., the increased incidence might be a consequence of new diagnostic procedures rather than a true increase in occurrence. This paper explores this issue in a French population.

Prostate cancer risk has been shown to be correlated with some food, sexual behaviour and a high intake of meat and a low consumption of vegetables and vitamin A [3]. Precocity and frequency of sexual intercourse have been found in other studies, and this might explain a lower incidence among Roman Catholic priests [8]. A genetic predisposition is strongly suggested by a higher frequency in some families and in some ethnic groups, e.g. negroid men in the U.S.A. Non-random chromosomal deletions in prostate cancer cells, some of them in the same chromosomes as well known anti-oncogenes, have been described [5]. However, none of these factors would yield a satisfactory explanation for such an observed increase in incidence rates as those that have been described [2, 4–7].

MATERIALS AND METHODS

Isère Cancer Registry is a population-based registry [1], covering a mixed urban and rural area with a population of 1 014 000 people (1990 census). The mean incidence per year for all cancers between 1983 and 1987 was of 1500 new cases for men and 1200 for females, with incidences, respectively, of 280

Correspondence to F. Ménégoz.
F Ménégoz, M. Colonna, C. Exbrayat and R. Schaerer are at the Registre du cancer de l'Isère, 21 chemin des Sources, 38240 Meylan; M. Mousseau, H. Orfeuvre and R. Schaerer are at the Service d'Oncologie Médicale, Centre Hospitalier Regional de Grenoble, France.
Revised 6 Sep. 1994; accepted 20 Sep. 1994.

and 200 per 100 000 people (World Standard). Standardised incidence rates for carcinoma of the prostate were computed for 12 years, from 1979 to 1990. Data on mortality in Isère were provided by the Institut National de la Statistique et de la Recherche Médicale (INSERM) in Paris.

We contacted the Urology department of the only hospital in the area, to verify if there were changes in the diagnostic procedures between 1983 and 1989. The annual number of transrectal needle biopsies during digital rectal examinations, the number of transrectal ultrasonography (TRUS) and the number of needle biopsies using ultrasonographic guidance were counted. We also contacted the Unit of Radioanalysis of the Institut Pasteur de Lyon (France) and the Radiopharmacology Unit of the Centre Hospitalier Universitaire de Grenoble to obtain annual frequencies of prostatic specific antigen (PSA) tests. Before the introduction of immunochemical procedures in 1988, PSA tests were not performed in other places in Isère.

A Poisson distribution of the incident cases was assumed, and trends were tested using a log-linear model. After adjustment for age, we extrapolated from the antilogarithm of the coefficient for the period, the mean increase of the incidence per year and its 95% confidence intervals.

RESULTS

During the 12 year period, 2239 cases of prostatic carcinomas were registered. In 1990, there were 297 new cases compared with only 136 in 1979. The crude incidence rate was 53.1 cases/100 000 men/year in 1988–1990, and 35.4 cases/100 000 men/year in 1979–1981, with a mean annual increase of 6.3% (range 4.9–7.8%). However, there was no notable increase until 1984 (Figure 1), whilst from 1985–1990 the mean increase per year was 10.6% (range 7.2–14.2%). This increase occurred for all age-groups, especially in the most recent period (1988–1990) (Figure 2). Variations in mortality (Figure 1), despite a small increase, were not significant (+ 1.3% (−0.3 + 3.0%)) over the study period.

353 cases of prostate carcinoma were detected, who, at the time of diagnosis, already had distant metastases and/or lymph node involvement. There was no increase in risk of advanced carcinoma between 1979–1990 (Figure 3). However, localised carcinoma of the prostate showed a notable increase of 7.6% each year, with a 95% confidence interval of 6.0–9.3.

Since the trend appeared to change after 1984, we contacted the Urology department of the main University Hospital of the area, in order to evaluate whether there were alterations to the diagnostic procedures that could explain the increase. TRUS was introduced in this department in 1984, but fully replaced digitally guided needle biopsy only in 1988 (Figure 4). During the same period, there was a steady increase in the number of patients submitted for biopsy, with a mean of 80 men each year between 1983 and 1987, and 160 men in 1989. PSA assays began in 1986 in one laboratory, and in 1987 in the other. A very high useage was reached in 1988, with more than 22 000 PSA tests in one laboratory, and almost 1000 in the other (Figure 5).

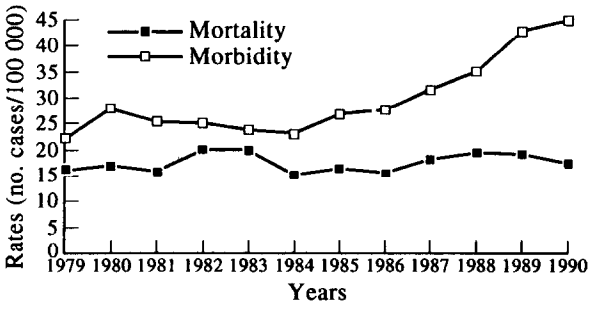

Figure 1. Incidence and mortality of carcinoma of the prostate between 1979 and 1990 in Isère, France (rates standardised for the world population).

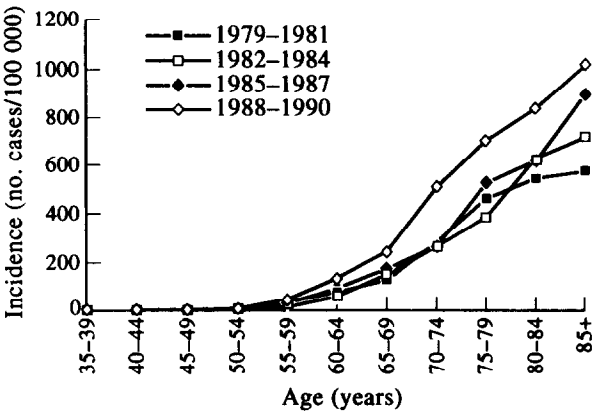

Figure 2. Age-specific rates of incidence of prostatic carcinoma in Isère for four time periods.

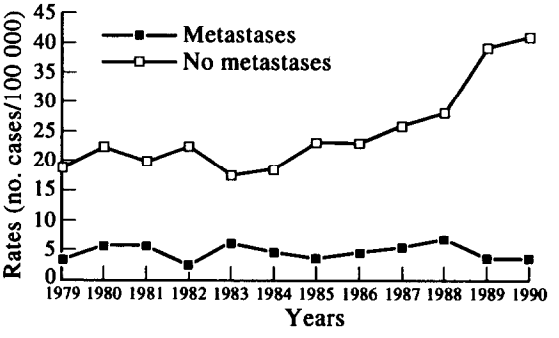

Figure 3. Incidence of prostatic carcinoma with and without metastases at diagnosis, from 1979 to 1990 in Isère, France.

DISCUSSION

Our work supports the recent results of a study based on the data of the SEER Programme [7], which showed an increase of the incidence of carcinoma of the prostate in the population of

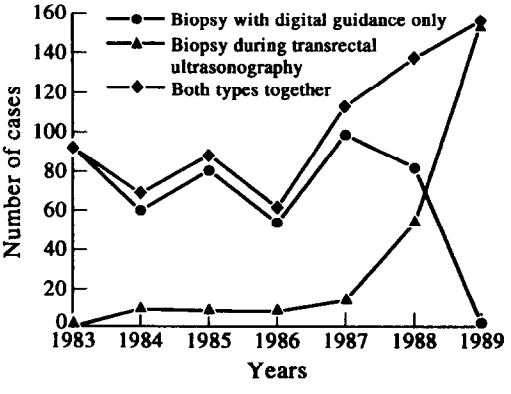

Figure 4. Use of transrectal ultrasonography for biopsy guidance at the University Hospital of Grenoble, France.

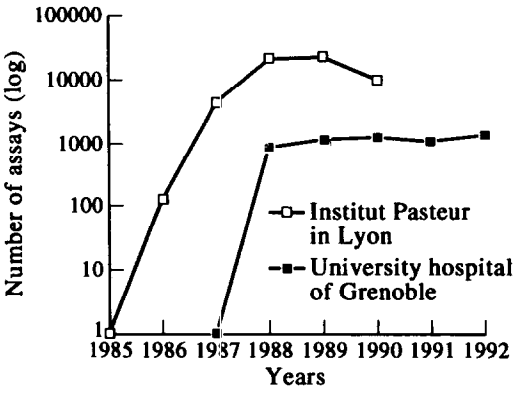

Figure 5. Radio-immunological assays of prostatic specific antigen in Urology departments in Isère, France, between 1986 and 1992.

the U.S.A. We have confirmed such an increase in a French population, with a similar rate of 6.3% (versus 6.4%) per year. We also found that, despite this sharp increase in incidence, there was no increase in mortality, which compares with a very small increase of mortality at the national level [9] for the period 1950–1985 in France. Increase of incidence both in the French and the U.S. population is restricted to localised carcinomas, as trends for cases with metastases showed no increase during that period of time. As the proposed explanation for such a situation [4–7] is that it could be related to changes in the diagnostic procedures, we tried to quantify the use of TRUS and PSA assays in our area.

The increase of 80% in prostatic biopsies (Figure 4) in conjunction with the increase of transrectal ultrasonography between 1987 and 1990 presented here is based on the activity of the Department of Urology of the University Hospital, which in this area, leads regarding new techniques. As a consequence, 1987 was the first year in which TRUS and guided biopsies were used in our area.

Because of French law, use of radioactive material for diagnostic purposes is limited, and in Isère, only two laboratories were allowed to perform radio-immunological assays of PSA between 1986 and 1992. Thus, there is almost a monopoly in terms of radio-immunological assays performed in this area, and therefore the information should not be biased. After rapid increases in the use of radio-immunological assays between 1986 and 1988 (Figure 5), a plateau was reached followed by reduction as a consequence of the introduction of other non-radioactive techniques, which began to be performed in other laboratories.

Increases in PSA assays and TRUS occurred in Isère in 1986–1988 which is also the period during which the increase in the incidence for carcinoma of the prostate began.

Currently, a causal relationship between this increase and the new means of diagnosis cannot be proved, although it can be hypothesised. Such an increasing morbidity between 1979 and 1990 is unique to prostate cancer in this area. As a result, this cancer moved from the third commonest in 1979–1982 to the second in 1987–1990, after lung, and before oral cavity and pharynx. The incidence of carcinoma of the prostate is increasing rapidly in most populations in Europe [3, 4], and mortality is also increasing, although less rapidly [9, 10]. Southern Europe, including Spain, Italy (Varèse), Portugal and France (Bas-Rhin) have no (or weak) increased mortality, but a very high increased incidence, exceeding 25% every 5 years (almost 20% every 5 years in France). This is the situation in Isère, with a 5 year increase in incidence of 33% and no increase in mortality. With 17 600 new prostate cancer cases in 1990 [2], France has the highest incidence among European countries, with an age-adjusted (World Standard) incidence of 40/100 000. This is far below the U.S.A., with rates of 61.8/100 000 in caucasian men and 82/100 000 in negroid men for the SEER Programme areas during 1983–1987 [7].

The simplistic explanation for this increase of incidence in the Southern Europe would be a true change in the risk of prostate cancer, but this is unlikely since there is no increase in mortality. In addition, in France, a parallel increase in mortality during the following 3-year period, which is more than the median survival of all stage patients in this country, was not observed. Thus, the only realistic explanation is a change in the diagnostic procedures. These have been widely influenced during the past decade by the increased use of both PSA and TRUS and, although there has been no consensus on adopted recommendations for the use of PSA as a screening procedure, many general practitioners in the study region do routinely prescribe this test to men over 50 years of age. Similarly, TRUS examination has become a more common procedure among urologists. This situation is very similar to that in the U.S.A. where both procedures together are widely used for early detection [11]. Thus, the augmentation of the morbidity rates is probably due to an increase of the number of small, non-symptomatic prostate cancers detected.

The influence of these new diagnostic procedures on the outcome of prostate cancer is still unknown. At best, it can be hoped that mortality will decrease, as diagnoses are made earlier, and that this will be proved by controlled clinical trials [12]. However, another possibility is that so called 'latent carcinomas' will be detected in asymptomatic patients, without any influence on their prognosis, and in this situation, one might expect to observe fallacious improvement of survival in clinical studies, as previously quiescent carcinomas are treated together with more advanced prostatic carcinomas. Analysing survival by stage can prevent this potential bias, as long as staging does not change in time (stage migration). Early detection could also increase the interval between diagnosis and death, with a resulting false improved survival. This lead-time bias might be difficult to counteract [13].

The steep increase in the incidence curve of the prostate carcinoma is of public health concern. If it is related only to the discovery of small cancers, which otherwise would have remained undetected, one of the effects of the new diagnostic methods would be to increase the burden of cancer in society, and to disturb unduly the lives of otherwise healthy people. As Lerner stated [14], 'Conventional teaching, based on historical studies of prostate, holds that patients with localised cancer seldom die as a direct consequence of the disease'. If we have confirmation in other countries that the increase of incidence is restricted to small, localised cancers, the question of treatment becomes an important issue, because of the high number of men who will be concerned by this situation [13, 14].

Only a decrease in mortality (a circumstance not so far observed in our area) would suggest a beneficial effect from new means of diagnosis. Thus, it is most important to carefully observe mortality for prostatic cancer within the next 5–10 years. Three different situations may arise: (a) a decrease of mortality, as a positive result of early detection of prostatic carcinoma; (b) an increase of mortality, the result of a real increase of the risk, although this looks rather unlikely; or (c) no change in mortality compared with the previous period of 20 years indicating no effect of new diagnostic methods.

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Acknowledgements—This work was supported by the French Ligue Nationale contre le Cancer, Comité de L'Isère (1993). We wish to thank Pr. C. Agnius-Delord who provided us with the information on radioimmunoassays of PSA in the Centre Hospitalier Universitaire of Grenoble, and Dr G. Charriere who gave us the same information from the Institut Pasteur in Lyon. We are also greatly indebted to Pr Rambeaud of the Urology department, who gave us access to the information on ultrasonography and needle biopsies.

Pergamon

European Journal of Cancer Vol. 31A, No. 1, pp. 58–63, 1995
Elsevier Science Ltd

0959–8049/95 $9.50+0.00

0959-8049(94)00372-6

A Retrospective Comparative Study Evaluating the Results of Mild Hyperthermic Versus Controlled Normothermic Perfusion for Recurrent Melanoma of the Extremities

J.M. Klaase, B.B.R. Kroon, A.M.M. Eggermont, A.N. van Geel, H. Schraffordt Koops, J. Oldhoff, D. Liénard, F.J. Lejeune, R. Berkel, H.R. Franklin and A.A.M. Hart

The aim of this study was to investigate the role of mild hyperthermia (39–40°C) in isolated cytostatic perfusion for patients with recurrent melanoma of the extremities. A total of 218 patients treated with mild hyperthermic perfusion was compared to 166 patients perfused under controlled normothermic conditions (37–38°C). Only patients whose lesions had been excised before or at the moment of perfusion were eligible for this study. A variety of prognostic factors was controlled for in a Cox proportional hazards analysis. The application of mild hyperthermia did not influence limb recurrence-free interval nor survival (corrected *P* values 0.46 and 0.18, respectively). In this retrospective comparative study, no benefit for mild hyperthermia in regional isolated perfusion could be identified.

Key words: regional isolated perfusion, recurrent melanoma, mild hyperthermia, melphalan
Eur J Cancer, Vol. 31A, No. 1, pp. 58–63, 1995

INTRODUCTION

NINE YEARS after Creech and colleagues developed the technique of regional isolated perfusion for melanoma patients [1], Cavaliere and associates, in 1967, introduced the idea of combining hyperthermia with this cytostatic treatment modality [2]. At first, temperatures of above 42°C were used but, although this resulted in encouraging antitumour effects, it soon became clear that the application of this so-called true hyperthermia was