Eur J Cancer, Vol. 29A, No. 5, pp. 745–749, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Cervical Cancer Incidence and Mortality Trends in Finland and Estonia: a Screened vs. an Unscreened Population

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Long term trends in the incidence of and mortality from invasive cervical cancer have been studied in Finland (1953–1987) and Estonia (1968–1987). The analyses are based on the data from the Finnish and Estonian Cancer Registries. An organised nationwide screening programme for cervical cancer was started in Finland in the early 1960s. In Estonia, no cytological screening programme has been introduced, and cervical malignancies are diagnosed in routine gynaecological practice. During 1968–1987, both the incidence of and mortality from cervical cancer were considerably higher in Estonia than in Finland. A decrease has taken place in the cervical cancer incidence and mortality in both countries since the mid-1960s, but whereas in Finland the decrease has been marked, in Estonia it has been less pronounced and levelled off in the 1980s. In 1987, the age-standardised (world population) incidence rate per 100 000 women was 14.0 in Estonia and 3.8 in Finland, and the age-standardised mortality rate was 6.0 and 1.6 per 100 000, respectively. The difference in the incidence of the disease in the two neighbouring countries can be partially attributed to socioeconomic factors. The main reason for the different slopes of the trend curves for cervical cancer is probably the difference in public health policies: an effective mass screening programme is being conducted in Finland but not in Estonia.
Eur J Cancer, Vol. 29A, No. 5, pp. 745–749, 1993.

INTRODUCTION

THE INCIDENCE of cervical cancer varies considerably both between populations [1] and within the same population [2]. The high incidence of cervical cancer has been observed for most developing countries. On the other hand, the data provided by cancer registries reveal differences between countries with similar health system development, but in which the extent of screening programmes for cervical cancer has been different [3]. In many countries throughout the world there has been a substantial decline in the incidence of and mortality from cervical cancer during the past 20–30 years [4, 5]. On the other hand, there is also recent evidence of an increase, especially in younger women [6].

The risk of cervical cancer is associated with the standard of living and socioeconomic status, and is probably mainly due to differences in sexual behaviour [7, 8]. The available epidemiological evidence indicates that the number of sexual partners both of women or their partners, the age at first intercourse, but also other variables such as smoking, long-term use of oral contraceptives, certain dietary factors and immunosuppression are the main determinants of cervical cancer risk [3]. However, the causal role of these factors is not established, and they should rather be considered as surrogate measures of the exposure to a sexually transmitted infectious agent.

The introduction of organised mass screening programmes has strongly affected the risk of invasive disease in many countries [9]. The Nordic trends in cervical cancer provide good evidence in favour of the efficacy of large-scale screening [10]. These programmes are uncommon in Central and Eastern Europe.

The aim of the present study was to compare the trends in cervical cancer in two neighbouring countries, in Finland and Estonia, and to relate the trends to the extent and intensity of the screening programmes.

In Finland (area 332 145 km^2), the total population was 4 938 602 and the female population was 2 545 700 in 1987; 94.0% of the total population were Finns. In Estonia (area 45 215 km^2), the total population was 1 552 169 and the female population was 828 308 in 1987; according to the 1989 census, 61.5% of the total population were Estonians and 30.3% Russians. Finns and Estonians have a close ethnic background. The cancer rates for Finland are closer to those for Estonia than to those for the other Nordic countries [11]. Cancer registration in Finland has a long tradition [12]. Finland is also one of the first countries to have a nationwide, population-based screening programme for cervical cancer [10].

Estonia was an independent country from 1918 to 1940 and a part of the U.S.S.R. from 1940 to 1991. Estonia is probably the only region of the former U.S.S.R. with a well-organised nationwide cancer registry, providing fairly reliable cancer statistics [13, 14]. An organised screening programme for cervical cancer was never introduced in Estonia.

MATERIALS AND METHODS

Cancer registration

The incidence and mortality statistics used in the study are based on the data of the Finnish and Estonian Cancer Registries. Both registries are population-based and cover the whole country. The cancer registration principles are basically the same in

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Revised and accepted 11 Nov. 1992.

Finland and Estonia, and the reporting of cancer cases is virtually complete [11].

The Finnish Cancer Registry (FCR) was established in 1952, and registration began in 1953. The FCR receives data on cancer cases from hospitals, health centres, medical practitioners, and pathological and cytological laboratories. It is also given information from all death certificates where cancer is mentioned. The coding of each cancer case is always evaluated by a pathologist. The file of all deaths occurring in Finland is annually checked against the files of the FCR [12].

The Estonian Cancer Registry (ECR) was established in 1978, but its records are retrospective to 1968, when the level of registration was already high enough for reliable cancer statistics to be calculated [15]. In Estonia, notification of new cancer cases is forwarded to 16 local cancer registries, from where the basic data are sent to the ECR. Data on cancer deaths are updated monthly in the ECR [16]. All death certificates with a cancer diagnosis filed with the Estonian State Department of Statistics are checked against the ECR files.

Mass screening

In Finland, organised nationwide cytological screening began in the 1960s. The general organisation of the programme and its results have been described elsewhere [10]. All Finnish women between the ages of 30 and 59 years are invited every 5 years to attend the screening. The age groups to be screened are chosen by the local municipal authorities, and there is some variation in the screened cohorts. The overall attendance rate is 70–80% [10, 17]. The results of screening and follow-up are reported to the Mass Screening Registry which operates at the FCR.

Cases included in the study

In this study, only invasive cervical cancer is considered. *In situ* lesions are not being registered in the ECR. During the period 1953–1987, 10454 new cases of invasive cervical cancer were diagnosed in Finland; among them, 4809 cases were diagnosed in 1968–1987. In Estonia, the number of new cases was 3498 in 1968–1987.

The total number of deaths from cervical cancer was 5167 in Finland in 1953–1987; among them, 2420 deaths occurred in 1968–1987. In Estonia, the number of deaths from cervical cancer was 1858 in 1968–1987.

In 1986, the proportion of histologically verified cases was 99% for Finland and 92% for Estonia.

Statistical analyses

The incidence and mortality rates have been standardised for age using the world standard population [1]. Standardisation was carried out for all ages together, and for the age groups of 20–34, 35–49, 50–64 and 65+. These truncated age-standardised rates are presented by the 5-year periods from 1968–1972 to 1983–1987.

The trends in the annual age-standardised rates are given for the period from 1953 to 1987 for Finland and from 1968 to 1987 for Estonia. The mean annual changes of the incidence and mortality rates for two separate 10-year periods, 1968–1977 and 1978–1987 have been estimated using the regression model:

$$\log y = a + bx.$$

RESULTS

The annual age-standardised incidence and mortality rates for cervical cancer are shown in Fig. 1. The rates were markedly higher in Estonia than in Finland. In Estonia, the age-standardised incidence rate per 100000 women was 22.3 in 1968, and 14.0 in 1987. In Finland, the rates were 13.6 and 3.8, respectively. There was a slight increase in the cervical cancer incidence in Finland up to the mid-1960s, followed by a rapid decrease. In Estonia, the incidence declined moderately from 1968 to the end of the 1970s, after which the decrease levelled off.

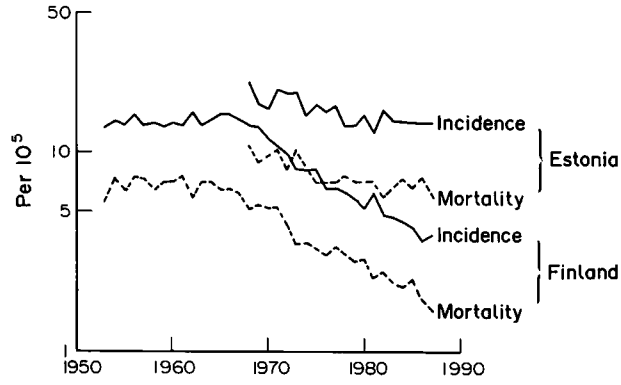

Fig. 1. Trends in the annual age-standardised incidence and mortality rates of cervical cancer in Finland, 1953–1987, and Estonia, 1968–1987.

The pattern for the mortality from cervical cancer is similar to that for the incidence. In Estonia, the age-standardised mortality rate per 100000 women was 10.6 in 1968, and 6.0 in 1987. For Finland, the rates were 5.1 and 1.6, respectively.

The mean annual changes in cervical cancer incidence and mortality in Finland were greater in 1968–1977 than in 1978–1987 (Table 1). In Estonia, after a moderate decline in the mean annual incidence during the first period, the trend was reversed in the latter period.

Table 2 shows the age-standardised incidence and mortality rates for the age groups 20–34, 35–49, 50–64 and 65+ in Estonia and Finland, in 1968–1972 and 1983–1987.

For all age groups, except for the 20–34 age group in 1968–1972, the risk of getting cervical cancer and dying from it was significantly higher in Estonia than in Finland. The differences in incidence and mortality rates have increased with time.

In Finland, the downward trend in the age-standardised incidence has been apparent for all age groups since the mid-1960s (Fig. 2). The relative changes have been greatest for women aged 35–49 and 50–64. In Estonia, the incidence increased for all age groups except 50–64 during the period 1983–1987. The increase was most conspicuous for the age group 35–49. Among women aged 20–34, the risk of cervical cancer was similar in Estonia and Finland in 1968–1972 (Table 2), but

Table 1. The mean annual change in cervical cancer incidence and mortality in Estonia and Finland, in 1968–1977 and 1978–1987

	Mean annual change (%)			
	Incidence		Mortality	
	1968–1977	1978–1987	1968–1977	1978–1987
Estonia	−2.3	0.4	−4.3*	−1.1
Finland	−8.4*	−5.6*	−7.0*	−6.1*

*$P < 0.05$.

Table 2. The age-standardised incidence and mortality rates of cervical cancer in Estonia and Finland, in 1968–1972 and 1983–1987, by age group (with a 95% confidence interval)

	1968–1972		1983–1987	
Age group	Estonia	Finland	Estonia	Finland
Incidence				
20–34	3.3	2.8	5.1	1.9
	(2.0–4.6)	(2.2–4.4)	(3.6–6.6)	(1.4–2.4)
35–49	39.5	24.7	22.5	5.6
	(35.1–43.9)	(22.6–26.8)	(19.2–25.8)	(4.7–6.5)
50–64	61.5	34.9	43.6	10.1
	(55.2–67.8)	(32.3–37.5)	(38.9–48.3)	(8.7–11.5)
65+	48.0	31.4	47.0	20.1
	(42.0–54.0)	(28.4–34.4)	(40.9–53.1)	(18.1–22.1)
Mortality				
20–34	0.6	0.4	1.8	0.3
	(0.1–1.1)	(0.3–0.5)	(1.0–2.6)	(0.1–0.5)
35–49	12.2	6.5	8.4	1.3
	(9.7–17.7)	(5.4–7.6)	(6.2–10.6)	(0.8–1.8)
50–64	33.7	17.4	19.0	4.7
	(29.0–38.4)	(15.6–19.2)	(15.9–22.1)	(3.8–5.6)
65+	37.2	21.6	33.2	15.8
	(32.0–42.4)	(19.1–24.1)	(28.2–38.2)	(14.7–17.5)

a continuous rise in the risk over time was seen in Estonia (Fig. 2).

Since the mid-1960s the most substantial reduction in mortality from cervical cancer has taken place in Finland for the age groups 35–49 and 50–64 (Table 2, Fig. 3). The decline in mortality rates over time was smaller for the other age groups.

In Estonia, a slight reduction in mortality rates occurred after 1968 for ages 50 and over (Fig. 3). On the other hand, there was a clearly increasing trend in cervical cancer mortality in 1983–1987 among women under 50.

DISCUSSION

The risk of cervical cancer is related to socioeconomic factors [2]. Differences between countries in social and economic development are usually correlated with the standard of living of people, their health habits and the quality of health services. Estonians and Finns are ethnically related, but Estonia lags markedly behind its neighbour both socially and economically

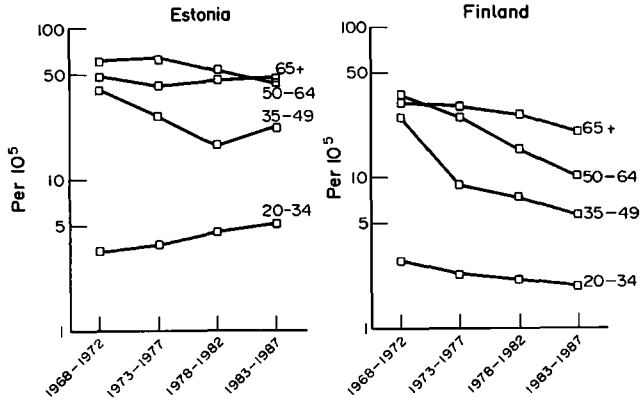

Fig. 2. Trends in the age-standardised incidence rates of cervical cancer in Estonia and Finland, in 1968–1987, by age group.

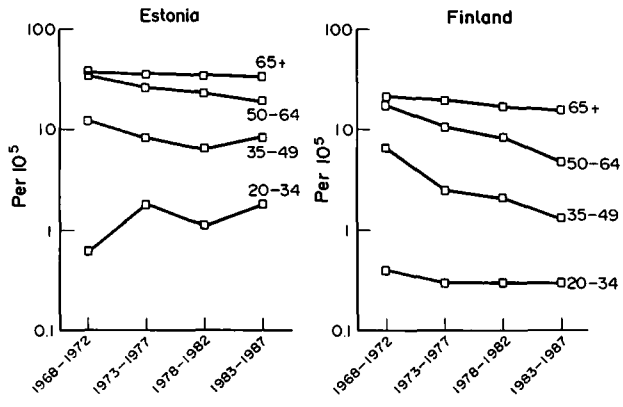

Fig. 3. Trends in the age-standardised mortality rates of cervical cancer in Estonia and Finland, in 1968–1987, by age group.

[14]. Therefore, the higher risk of cervical cancer in Estonia can be partially attributable to these differences. Reliable cancer statistics for Estonia are available from 1968, but there are grounds to assume that mortality from the disease was substantially higher in Estonia than in Finland during the period before 1968. This indicates that the nationwide screening programme for cervical cancer began in Finland at overall lower rates than those for the same period in Estonia.

The association between standard of living and risk of cervical cancer is mostly attributable to sexual behaviour, but also other factors such as smoking and the use of oral contraceptives [3]. The incidence of cervical cancer was similar in Estonia and in Finland for women aged less than 35 years before the start of organised mass screening in Finland. Therefore, it can be assumed that differences in sexual habits between the countries do not account for the much higher risk of cervical cancer in Estonia.

The role of cigarette smoking in the aetiology of cervical cancer is currently debated. The basic question is whether the association of smoking and cervical cancer is causal or artifactual, produced by some extraneous confounding difference between smokers and non-smokers [18]. In 1979, the proportion of daily smokers among females was about 18% in Estonia [19] and 16% in Finland [20]. Thus, the susbtantial difference in cervical cancer risk cannot either be explained by the differences in the prevalence of cigarette smoking.

The association between oral contraceptives and the risk of cervical cancer has been the subject of numerous studies which have yielded conflicting results [3]. In Finland, 17% of women aged 18–44 used oral contraceptives in 1971 and 18% in 1987 [21]. There is no direct data about the use of oral contraceptives in Estonia, but during the period under study, it was probably lower in Estonia than in Finland and other western countries. The shortage of available contraceptives and uncertainty about their reliability has left most Soviet women with other alternatives to regulate their fertility. Based on the results of the Soviet Interview Project G1 Survey [22], only 7.1% of women had ever used oral contraceptives. Abortion has been the primary method of fertility control in the U.S.S.R. since at least the 1960s. In 1980, the abortion rate per 1000 women aged 15 to 49 was 96.7 in Estonia [23] and only 12.3 in Finland (calculated on the basis of [24]).

In some countries, the increasing frequency of hysterectomies has caused an underestimation of the risk of cervical cancer [25]. The hysterectomy rates vary considerably between countries.

The prevalence of total hysterectomies was about 2-fold lower in Finland in 1987–1988 than in the United States in 1985 [26]. The age-specific prevalence of hysterectomies was recently obtained from a questionnaire sent to a random sample of Finnish women aged 45–64. One-fifth of the women who responded had had a hysterectomy [26]. No data directly measuring the prevalence of total hysterectomy have been reported for Estonia, but it is known that this surgery is not very widely used as a method of producing artificial menopause. In Estonia, the number of total hysterectomies was 476 in 1991 (Bureau of Medical Statistics, unpublished data). The adjustment for age-specific fractions of women who have had a hysterectomy could have a certain influence to the cervical cancer rates in both countries but it is unlikely that it could have much influence to the differences stated between the countries.

There is now worldwide evidence of a considerable decline in incidence and mortality from cervical cancer in areas with active mass screening programmes. However, the efficacy of these programmes has varied, and the trends in the disease have not been substantially affected by screening in some countries. In the Nordic countries, there was an increase in the incidence of cervical cancer up to the mid-1960s. Finland, Iceland and Sweden introduced nationwide screening programmes in the early 1960s. After their introduction, a reduction in the incidence of and mortality from invasive cervical cancer was observed, specifically in the age span at which the screening was targeted. A marked decrease in rates was also seen in Denmark, where a screening programme was initially introduced in selected counties. In Norway, the organised screening programme covers only one county, and the incidence of cervical cancer showed an increasing trend up to the mid-1970s, since when a slight decrease has been reported [10].

Estonia is a former region of the U.S.S.R. During the study period, health care organisation in Estonia was rather similar to that in the other regions of the U.S.S.R. According to the directives of the old centralised health care system, each woman over the age of 18 years should be examined by a gynaecologist at least once a year, and a cytological investigation should be performed [27]. Unfortunately, this "norm" was not applied in reality and there was substantial variation in the frequency and completeness of the examinations. Usually a Pap smear was taken only if specially requested. This was also the case in Estonia, where Pap smears were taken only within the framework of routine gynaecological practice, mainly after the appearance of clinical indications. The exact number of smears taken by gynaecological units is not documented, but it is assumed that one smear was taken for each hospital patient admitted with a gynaecological diagnosis. Thus, the smear-taking frequency per woman varies over a very large range, as does the frequency of gynaecological examinations.

As any influence from an organised screening programme for cervical cancer is lacking in Estonia, and there have been no marked changes in diagnostic and treatment efficacy since 1968 [28], the trends in incidence and mortality probably indicate changes in the risk factors. However, there is no clear evidence of an increasing role of any sexually transmitted infection. It is not likely that sexually transmitted viral infections were much more frequent in Estonia than in Finland.

The rapid decline in the incidence of and mortality from cervical cancer in Finland after the introduction of the screening programme has led to a continuous widening of the gap between the rates for Finland and Estonia. This difference is most evident for the ages targeted by screening in Finland. Thus, the main reason for the difference in the trends in incidence and mortality from cervical cancer is likely to be the differences in public health policy in these two neighbouring countries.

Finally, the target of the organised screening programme in Finland is the unselected total population, and the individuals are invited to participate in the screening programme by the health authorities. In contrast, the random smear-taking practice in Estonia is likely to increase the inequality in health status, because it depends on a woman's age, awareness and health education. The routine gynaecological examinations are not likely to catch those people who would really benefit from regular screening, e.g. middle-aged and older women with a high risk of developing cervical cancer.

1. Muir C, Waterhouse J, Mack T, Powell J, Whelan S, eds. *Cancer Incidence in Five Continents*, Vol. 5. Lyon, IARC Scientific Publications No 88, 1987.
2. Hakama M, Hakulinen T, Pukkala E, Saxén E, Teppo L. Risk indicators of breast and cervical cancer on ecologic and individual levels. *Am J Epid* 1982, **116**, 990–1000.
3. Muñoz N, Bosch FX. Epidemiology of cervical cancer. In Muñoz N, Bosch FX, Jensen OM, eds. *Human Papillomavirus and Cervical Cancer*. Lyon, IARC Scientific Publication No 94, 1989, 9–39.
4. Stukonis MK. *Cancer Incidence Cumulative Rates—International Comparison Based on Data from "Cancer Incidence in Five Continents"*. Lyon, IARC Internal Technical Report No 78/002, 1978, 27.
5. Cuzick J, Boyle P. Trends in cervix cancer mortality. *Cancer Surveys* 1988, 7, 417–439.
6. Cook GA, Draper GJ. Trends in cervical cancer and carcinoma *in situ* in Great Britain. *Br J Cancer* 1984, **50**, 367–375.
7. Buckley JD, Harris RWC, Doll R, Vessey MP, Williams PT. Case–control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 1981, ii, 1010–1014.
8. Kjaer SK, de Villiers EM, Dahl C, *et al.* Case–control study of risk factors for cervical neoplasia in Denmark. I: Role of the "male factor" in women with one lifetime sexual partner. *Int J Cancer* 1991, **48**, 39–44.
9. Hakama M, Miller AB, Day NE, eds. *Screening for Cancer of the Uterine Cervix*. Lyon, IARC Sci Publ No 76, 1986.
10. Hakama M, Magnus K, Pettersson F, Storm H, Tulinius H. Effect of organized screening on the risk of cervical cancer in the Nordic countries. In Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC, eds. *Cancer Screening*. Cambridge, University Press, 1991, 153–162.
11. Hakulinen T, Rahu M, Aareleid T, Pukkala E, Teppo L, Vanaselja T. Syöpä Suomessa ja Virossa. *Duodecim* 1983, **99**, 1741–1751.
12. Saxén E, Teppo L. *Finnish Cancer Registry* 1952–1977. *Twenty Years of a Nationwide Cancer Registry*. Helsinki, Finnish Cancer Registry, 1978.
13. Rahu M, Aareleid T. *Vähk Eestis/Cancer in Estonia. Diagrammid/Diagrams*. Cancer Society of Finland Publication No 44. Helsinki, Estonian Cancer Registry and Finnish Cancer Registry, 1990.
14. Aareleid T, Rahu M. Cancer survival in Estonia from 1978 to 1987. *Cancer* 1991, **68**, 2088–2092.
15. Aareleid T. Survival patterns of female breast cancer patients in the Estonian SSR in 1968–1981. *Neoplasma* 1985, **32**, 257–263.
16. Karjalainen S, Aareleid T, Hakulinen T, Pukkala E, Rahu M, Tekkel M. Survival of female breast cancer patients in Finland and in Estonia: stage at diagnosis important determinant of the difference between countries. *Soc Sci Med* 1989, **28**, 233–238.
17. Hakama M, Räsänen-Virtanen U. Effect of a mass screening program on the risk of cervical cancer. *Am J Epidemiol* 1976, **103**, 512–517.
18. Layde PM. Smoking and cervical cancer: cause or coincidence? *JAMA* 1989, **261**, 1631–1633.
19. Raudsepp J. *Tubakakatk*. Tallinn, Valgus, 1980, 18.
20. Central Statistical Office of Finland: Tobacco Statistics 1990. Official Statistics of Finland. *Health* 1991, **2**, 18.
21. Makkonen K, Hemminki E. Different contraceptive practices: use of contraceptives in Finland and other Nordic countries in the 1970s and 1980s. *Scand J Soc Med* 1991, **19**, 32–38.

22. Anderson BA. *The Role of Abortion in Fertility Decisions in the Soviet Union: Results from Analysis of Data from Soviet Emigres.* Research Report No 91-231. University of Michigan, Population Studies Center, 1991.
23. Statistika aastaraamat 1991. Tallinn, Eesti Vabariigi Riiklik Statisktikaamet, 1991.
24. Miettinen A. Population data on Finland 1900–1991. In Lindgren J, ed. *Yearbook of Population Research in Finland XXIX* 1991. Helsinki, The Population Research Institute, 1991, 142–151.
25. Howe HL. Age-specific hysterectomy and oophorectomy prevalence rates and the risks for cancer of the reproductive system. *Am J Publ Health* 1984, **74**, 560–563.
26. Luoto R, Hemminki E, Topo P, Uutela A, Kangas I. Kohdunpoistoleikkauksen esiintyvyys ja taustatekijät Suomessa. *Sosiaalilääketieteellinen Aikakauslehti* 1992, **29**, 104–112.
27. Ministry of Health of the U.S.S.R. Directive No 430, 22 Apr 1981: Instructions about the Organization of the Gynaecologic Consultation. Moscow, Ministry of Health of the U.S.S.R., 1981 (in Russian).
28. Aareleid T. Patient Survival in Cancer of the Stomach, Lung, Breast and Cervix Uteri in the Estonian SSR (Estonian Cancer Registry Data, 1968–1981). Abstract of PhD (CandSc) thesis. Moscow, All-Union Cancer Research Center, 1988 (in Russian).

Acknowledgements—The authors thank Dr Lyly Teppo, the director of the Finnish Cancer Registry, and Mr Mati Rahu, the scientific adviser of the Estonian Cancer Registry for helpful discussions during preparation of the manuscript. We would also like to thank two unknown referees for their valuable comments. This work was a part of the co-operation project between the Finnish and Estonian cancer registries.

Eur J Cancer, Vol. 29A, No. 5, pp. 749–753, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Expression of c-*erb*B-2 Oncoprotein in Transitional Cell Bladder Cancer

P. Lipponen

Paraffin embedded tissue from 249 transitional cell bladder cancers (TCC) was stained by an antibody against c-*erb*B-2 oncoprotein to evaluate its overexpression. The staining results were related to histopathological features and clinical follow-up data. 99/249 (39%) of tumours were positive for c-*erb*B-2 oncoprotein and 31/249 (12.5%) of them showed moderate or heavy staining. c-*erb*B-2 overexpression was related to pelvic lymph node involvement ($P = 0.0355$) and distant metastasis ($P = 0.0058$) at the time of diagnosis, whereas no significant relationship was found between T-category and c-*erb*B-2 oncoprotein overexpression. Expression of c-*erb*B-2 was related to high WHO grade ($P = 0.0033$), DNA aneuploidy ($P = 0.0061$), high S-phase fraction ($P = 0.042$), and several morphometric nuclear factors ($P = 0.01$–0.09). All the tumours with high levels of c-*erb*B-2 expression were tetraploid in flow cytometry ($P < 0.0001$). c-*erb*B-2 expression predicted recurrence-free survival in superficial tumours ($P = 0.057$) and in survival analysis moderate or intense expression of c-*erb*B-2 oncoprotein was related to decreased survival probability ($P = 0.27$). In multivariate survival analysis overexpression of c-*erb*B-2 had no independent prognostic value. The results show that immunohistochemical demonstration of c-*erb*B-2 oncoprotein overexpression in paraffin embedded archival material has no prognostic value over already established predictors in TCC.
Eur J Cancer, Vol. 29A, No. 5, pp. 749–753 1993.

INTRODUCTION

PROTO-ONCOGENES encode proteins that have a normal function, but when these genes are altered or expressed abnormally they are thought to contribute to the pathogenesis of cancer [1]. The proto-oncogene c-*erb*B-2 encodes a transmembrane growth factor receptor with significant sequence homology to the epidermal growth factor receptor, although they are not identical [2, 3]. Overexpression of the c-*erb*B-2/*neu* gene has been observed in breast [4, 5], ovarian [4] and lung [6] tumours and also in transitional cell bladder cancer (TCC) [7–11]. In breast [4, 5, 12, 13] and in ovarian [4] tumours amplification of c-*erb*B-2/*neu* is related to unfavourable prognosis, but the results are controversial. Alterations in oncogenes and oncoproteins have also been reported in bladder tumours [10–12] and there is a correlation between muscle invasive potential and epidermal growth factor receptors [15]. The importance of c-*erb*B-2 expression has not yet been fully evaluated in comparison to established prognostic factors in TCC and accordingly the aim of the present study was to investigate the expression of the c-*erb*B-2 oncoprotein in TCC. The results were correlated to previously characterised prognostic factors and clinical behaviour of TCC in a cohort of 249 patients followed-up for over 10 years.

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Revised 14 Oct. 1992; accepted 3 Nov. 1992.

PATIENTS AND METHODS

Patients

249 patients with a newly diagnosed TCC were followed-up for a mean of 10.9 years (range 9.4–22 years) during 1965–1991. There were 199 males and 50 females and their mean age was 67 years at the time of diagnosis. The diagnosis, treatment and