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SURVIVAL RATES IN LUNG CANCER PATIENTS WITH AND WITHOUT BRONCHIAL ASTHMA

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Bronchial asthma itself or the treatment of asthma may modify the immunological response to cancer. The survival of lung cancer patients with a preceding diagnosis of bronchial asthma was compared with that of non-asthmatic lung cancer patients in Finland during 1970–1989. This was accomplished by linking two nation-wide data registers, the medication reimbursement register and the cancer registry. For 921 out of the 926 asthmatic patients with lung cancer diagnosed after the diagnosis of bronchial asthma, a non-asthmatic referent patient, matching with respect to sex, anatomical site, and histological type of tumour, as well as to age and year of lung cancer diagnosis, was successfully found in the files of the Cancer Registry. Another referent group was formed by using the stage of lung cancer at diagnosis as an extra matching criterion; this search was successful for 895 asthmatic lung cancer patients. The corrected 5-year survival rate of asthmatic lung cancer patients was 8.4% and that of the referent patients, not matched for stage, 9.6%. When stage was included as matching criterion the corresponding rates were 8.5% and 8.1% respectively. None of these differences were significant. The prognosis of asthmatic and non-asthmatic lung cancer patients thus seemed to be similar.

A recent study of cancer risk among 77 952 asthma patients in Finland showed that both male and female asthma patients had a higher risk of lung cancer than the general population, the age-standardized incidence ratios being 1.32 and 1.66 respectively (Vesterinen E et al., submitted for publication).

Risk factors of cancer are not usually the same as prognostic factors. Although patients with asthma may have a higher risk of dying from lung cancer (1–3), it does not necessarily imply preceding asthma diagnosis as an indicator of poor prognosis in lung cancer. There are several reasons why asthmatic lung cancer patients could have survival rates different from those of other lung cancer patients. The histological distribution of malignant lung tumours in asthma patients is somewhat different from the general pattern (Vesterinen E et al., submitted for publication). Regular check-ups of patients suffering from asthma may lead to earlier diagnosis of lung cancer and consequently improved survival. Asthma and the pulmonary hypersensitivity reaction are associated with augmentation of the natural killer cells in the peripheral blood (4, 5) which constitute an important defence mechanism against cancer (6) and might slow down the progress of cancer. On the other hand, corticosteroids used for the treatment of asthma, may suppress the immune system (7) and hasten the growth of cancer. It has also been reported that cellular cytotoxic activity in lung cancer patients has a prognostic significance, especially in stages II–IV (8).

The purpose of the present study was to compare the prognosis of lung cancer patients with and without asthma respectively.

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Materials and Methods

Finnish Cancer Registry. All hospitals, medical practitioners, and institutions with hospital beds in Finland are obliged to notify the Finnish Cancer Registry (founded in 1952) of all cancer cases that come to their attention. Moreover, the pathology laboratories inform the registry on all tissue and cytologic specimens with a diagnosis of cancer. The Central Statistical Office reports to the registry whenever cancer is mentioned on a death certificate. The Central Statistical Office files are also used to follow the patients as regards death or emigration. On an average five notifications per case are received during the various phases of the disease. Checks have indicated that the registration has a high degree of completeness (9).

Record linkage with the Social Insurance Institution files. In Finland, all residents of the country are covered by the National Sickness Insurance. Since 1970 the National Sickness Insurance has covered 90 or 100% of the costs of drug treatment for chronic bronchial asthma. Patients meeting stringent diagnostic criteria (Table) are eligible for this benefit and are registered by the Social Insurance Institution. All patients who were entitled to 90 or 100% reimbursement of the costs for bronchial asthma medicine in 1970–1989 were identified in the nation-wide Social Insurance Institution register. Making use of the unique personal identification number (issued to all residents in Finland), the Social Insurance Institution files of asthma patients were linked to the lung cancer cases diagnosed in 1970–1989. This procedure led to identification of 1 464 asthma patients with lung cancer. In 538 cases, the diagnosis of lung cancer was made during the same month, or even earlier, as the right to reimbursed medication was granted. These cases were excluded from the analysis due to selection bias: all had survived at least from lung cancer diagnosis till asthma reimbursement. Thus, 926 patients were included in the analysis.

Table

The diagnostic criteria according to which the right to reimbursed medication is granted to patients with bronchial asthma

Pulmonary function
- FEV1* or peak expiratory flow (PEF) value increases with a bronchodilating drug 15% or more, in adults at least 0.15 l or 50 l/min,
- after the exercise FEV1 or PEF value decreases 15% or more from the starting point, in adults at least 0.15 l or 50 l/min, and
- in PEF values measured between 4 and 6 h during one day a variation more than 20% must be found.

In addition, the results of skin test and bronchial challenges (specific and non-specific challenges) may be considered in granting the right for reimbursement.

*FEV1 = forced expiratory volume in one second

Referent populations. Two different referent groups of lung cancer patients were selected from the files of the Finnish Cancer Registry. Members of the referent populations were individually matched with members of the 926 asthmatic lung cancer patients. The referent patient was randomly selected from the group of patients fulfilling the matching criteria. In the first referent group, the referents were matched by the following criteria: sex, subsite (trachea, lung, pleura), histological tumour type, age at diagnosis of lung cancer (± 5 years) and year of diagnosis (± 1 year). Six categories were used in matching the histological type: adenocarcinoma, squamous cell carcinoma, epidermoid carcinoma NOS, small cell carcinoma, other histological type, and no histology. Referents were found for the 921 asthmatic lung cancer patients (771 males and 150 females). In order to control for differences in stage distribution stage was added as an extra matching criterion when the second referent group was formed. Five categories of stage were used: 1) localized, 2) tumour had spread to local lymph nodes, 3) tumour had metastasized and/or infiltrated adjacent tissues, 4) tumour had metastasized and/or infiltrated other tissues but the extent was not known, and 5) stage was unknown or had not been reported to the registry. With this additional matching it was possible to find a referent for 895 asthmatic lung cancer patients (762 males and 133 females). All the codes for the subsite, histological type and the stage were those routinely coded by the Finnish Cancer Registry and thus independent of the fact whether a patient had asthma or not.

Follow-up of patients. The patients were followed up for death or emigration through the files of the Central Statistical Office and Population Register Center. All patients could be followed until 31 December, 1990 or to the death of the patient.

Statistical methods. Survival of lung cancer patients was measured using the corrected survival rate. Not all the deaths of cancer patients were due to the cancer in question. Therefore, a measure of survival which takes the extraneous mortality from other causes of death into account had to be used. The corrected survival rate was estimated as the observed survival with the exception that patients dying from causes other than lung cancer were regarded as withdrawals (10, 11). Information on the reported underlying cause of death was used to decide whether the death was due to lung cancer or to another disease. Also, this coding is part of the routine of the Finnish Cancer Registry and thus not dependent on the asthma status of the lung cancer patients. The corrected survival rates were calculated using the actuarial method, and their standard errors with Greenwood's formula (12). In order to compare the differences in survival rates, the sign test (13) was carried out.

Results

Distribution of the matching criteria in the material. In the referent group not matched for stage there were 771

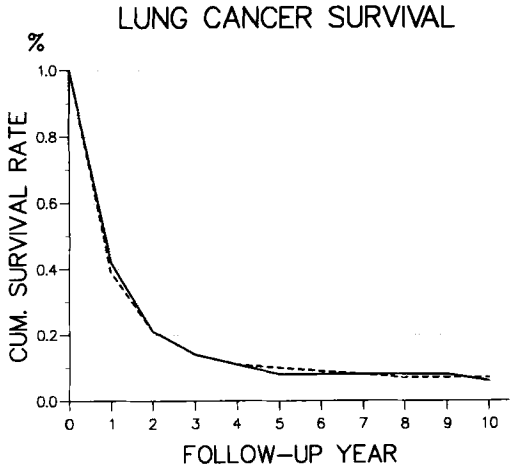

Figure. The cumulative corrected survival rates of 921 asthmatic lung cancer patients and their individually matched non-asthmatic referent patients with lung cancer in 1970–1989 in Finland. Matching criteria for the referent patients: sex, subsite, histological type of the tumour, age at diagnosis of lung cancer (±5 years) and year of diagnosis (±1 year). —— asthma; – – – no asthma.

male and 150 female patients of which 40% were under 65 years of age. The histological types were: 11.9% adenocarcinoma, 27.7% squamous cell carcinoma, 11.2% small cell carcinoma, 12.3% epidermoid carcinoma NOS, 2.6% other histological types and 34.3% without histologic diagnosis. There were only 9 cases of carcinoma in trachea and pleura, while in the remaining cases, lung had been reported as primary site. The stage distribution (cf. above) was: 1) 24.0%, 2) 27.7%, 3) 7.5%, 4) 33.8% and 5) 7.1%. Cancer was localized in 28% of the patients with asthma and in 24% of those without asthma. The autopsy rate in patients with asthma was 22% and in those without asthma 20%.

Comparison with the referent group not matched for stage. The mean age at diagnosis of lung cancer was 66.5 years for both asthmatic and non-asthmatic patients. The survival rates of the asthmatic patients were slightly lower, but did not differ significantly from those of the non-asthmatic referent patients during the first 10 years of follow-up after diagnosis of lung cancer (Figure). The 5-year cumulative corrected survival rate was 8.4% (95% CI 6.3–10.5%) for asthmatic patients and 9.6% (7.5–11.8%) for non-asthmatic patients. The 10-year corrected survival rates were 6.5% (3.9–9.0%) and 6.5% (4.2–8.8%) respectively. In the sign test, the χ^2 value was 0.115, which is not significant with one degree of freedom. In men, the 5-year corrected survival rate for asthmatic patients was 8.1% (5.8–10.4%) and for non-asthmatic patients 9.9% (7.4–12.3%). In women, the corresponding rates were 10.2% (4.6–15.8%) and 8.4% (3.6–13.1%) respectively.

Comparison with the referent group matched for stage. When the matching criteria of the referent patients included the stage at diagnosis the asthmatic patients had slightly higher survival rates, although the difference was non-significant. The 5-year corrected survival rate was 8.5% (6.3–10.7%) for asthmatic patients and 8.1% (6.0–10.2%) for non-asthmatic ones. The χ^2-value of the sign test was 0.001 (one degree of freedom, non-significant). The 10-year corrected survival rates were 7.2% (4.7–9.6%) and 5.5% (3.3–7.7%) respectively. In men, the 5-year corrected survival rate for asthmatic patients was 8.1% (5.8–10.4%) and for non-asthmatic patients 8.2% (5.9–10.5%). In women, the rates were 10.8% (4.7–16.9%) and 8.2% (3.0–13.5%) respectively.

Comparison within the histological subgroups. Concerning histological subgroups, with and without matching for stage, no significant survival differences were found between asthmatic and non-asthmatic patients (sign test).

Discussion

Patients with bronchial asthma before the diagnosis of lung cancer had very similar survival rates as individually matched non-asthmatic referent lung cancer patients, regardless whether the referent patients were matched for stage or not. Asthmatic patients have a more unfavourable distribution of histologic tumour types than lung cancer patients without preceding asthma with epidermoid carcinomas and adenocarcinomas being overrepresented among asthmatic patients (Vesterinen E et al., submitted for publication). This was, however, taken into account by matching by histological type.

The use of corrected survival rates requires reliability as to the information on cause of death. The Finnish Cancer Registry's information on deaths of cancer patients is more accurate than that given in the official death certificates. The Finnish Cancer Registry receives on an average five notifications per case from different sources, after which the pathologist in the cancer register decides whether a patient has died from cancer or not. This corrected information has previously been used in a study on breast and intestinal cancer (14) and was used in the present study too.

We were especially interested in survival differences which could be related to variations in the immunological response to cancer, caused by asthma itself, or by treatment of asthma. We tried to eliminate the effect of other prognostic factors using specific matching criteria for selection of referent patients. The respiratory organs of asthma patients are regularly examined, which could lead to earlier diagnosis of respiratory malignancies. Studies on the effectiveness of screening of lung cancer have shown that earlier diagnosis may lead to improved survival during the early follow-up but it does not decrease the more long-term mortality (15, 16). This kind of survival improvement is probably a lead-time effect without real improvement of the prognosis.

Stage at diagnosis was added as an extra matching criterion to form a second referent population. Stage at

diagnosis is associated both with tumour aggressiveness and diagnostic delay and may, or may not, reflect the effectiveness of immune response to the tumour. Comparison with this referent population however, gave very similar result—asthma did not significantly influence the survival of lung cancer patients.

Asthma and pulmonary hypersensitivity reaction are associated with augmentation of natural killer cells in peripheral blood (4, 5) and might thus inhibit the progress of cancer. On the other hand systemic corticosteroids used for treatment of asthma may suppress the immune system (7) and hasten the progress of cancer. As we found no difference between the survival of asthmatic lung cancer patients and control patients, it could be hypothesized that positive and negative immunological effects in asthma neutralize each other in the control of the malignant growth. Alternatively—and perhaps more probably—immune response is not very important for the outcome of lung cancer. Another reason for the lack of difference may be the almost invariable poor prognosis of lung cancer which may make it difficult to observe a small survival difference between the groups.

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