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Cancer risk in asthmatic subjects selected from hospital discharge registry

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Cancer risk in asthmatic subjects selected from hospital discharge registry. B. Källén, J. Gunnarskog, T-B. Conradson. ©ERS Journal Ltd 1993.

ABSTRACT: We wanted to study cancer risk in asthmatic subjects.

With the use of central health registries, a cohort of 64,346 patients, treated in hospital with an asthma diagnosis, was followed with respect to cancer development. The observed numbers of different types of cancer were compared with the expected numbers, estimated from population data, with consideration taken to patient age, sex, survival, and the year of diagnosis.

In general, a marked reduction of cancer incidence (2 out of 3 of the expected numbers) was found, with the exception of two cancer types: cancer of the respiratory tract and cancer of endocrine glands. A more noticeable reduction in cancer risk was seen for multiple myeloma, malignant melanoma, mammary cancer, uterine body cancer, and stomach cancer.

The causes of this "protective effect" are not indicated by the present analysis, and need further study.

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A study in 1960 [1], first indicated that allergic conditions, including asthma, could have a protective effect on cancer development. Since then, a number of studies have been published. A summary of 16 studies was published in 1985 [2]. The majority of these were retrospective case-control studies. Only three cohort studies were listed and the observed numbers of cancer were low: 63 [3], 26 [4], and 328 [5]. The association between asthma and cancer was thought, in two articles, to be protective, but the findings of the third study were contradictory.

An interview study [2] of 13,665 cancer cases, and 4,079 non-neoplastic controls, who were admitted to one hospital from 1957–1965, showed a suggested reduction in cancer odds ratio in asthma and hay fever (after adjusting for age and smoking habits), but found a more marked decrease associated with a history of hives and other allergy-related diseases. One exception was pulmonary cancer, which was increased after asthma, a finding further supported by a prospective study in California (based on five observed male and one female pulmonary cancer among patients with asthma) [6]. The conclusion of this study was that individuals with allergy-related disorders may have a decreased risk of cancer.

Since that paper, a specific investigation of the possible association between melanoma and atopic diseases has been published [7], again a retrospective case-control study based on 331 melanoma patients and 380 control subjects. This study found an association between atopic disease and a reduced melanoma risk. A recent prospective study of allergy and cancer in Seventh-day Adventists in California [8] found a nonsignificant decrease in the relative risk for all cancers in males; the relatively small size of the study population resulted in wide confidence intervals when specific sites were analysed.

We have studied the specific problem of an association between asthma and cancer risk using computerized health registries available in Sweden. In this way, a large cohort of patients, treated in hospital for asthma, was studied with respect to cancer development.

Patients and material

In Sweden, a set of health registries exists, which can be linked with the use of the unique personal identification number that each citizen gets shortly after birth and keeps unchanged all life, and which is extensively used in society, including health care. Each number contains a check digit, which makes it possible to detect errors. Such registries have been extensively used in epidemiological studies of health problems, including cancer. In the present study, three registries were used:

1. The Hospital Discharge Registry (National Board of Health), which covers about 80% of the country (some counties being excluded), and consists of computerized discharge diagnoses (International Classification of Diseases (ICD) 8 codes) of patients treated in public hospitals. Information also includes date of discharge and the personal identification number. Data for 1969–1984 were used (from 1984 onwards, identification numbers were removed from the register).

2. The Swedish Cancer Registry (National Board of Health), which covers the whole of Sweden and contains all patients with a diagnosed cancer. The register is a tumour register, each identified tumour representing one case. The information includes cancer diagnosis (ICD 7 codes), date of diagnosis, and the personal identification number. The latter have been extensively checked and very few errors exist. Data for the years 1958–1987 were used.

3. The Death Registry (Statistics Sweden), which contains date of death and the personal identification number for each person dying in Sweden. The accuracy of the latter is close to 100%. Deaths up to December 31, 1987 were identified.

Methods

From the Hospital Discharge Registry, all patients treated for asthma during 1969–1983 were identified. A total of 264,761 treatment periods were identified among 64,400 patients. In some patients, however, errors had occurred in the identification number (which contains a check figure), and, after removal of these, 64,346 remained.

This cohort was linked to the Cancer Registry. In this way, we identified 7,452 patients who had both been treated in hospital for asthma and who had developed cancer. The cancer diagnosis had sometimes been made before the first known treatment period for asthma (obviously the patients could have had the disease before that time), but the continued study was restricted to the 4,520 cancer cases (2,641 tumours in men and 1,879 in women) in a total of 4,275 patients, which occurred after the first known hospital treatment period for asthma. Only malignant conditions were included.

The total asthma cohort was linked with the Death Registry, and the date of death was transferred. In this way, we identified all patients who had died within the country before the end of 1987.

From the total Cancer Registry, the expected number of cancer diagnoses was calculated for the total asthma cohort from the time of the first asthma treatment period registered. The total cancer rate (age, sex and type specific) for each year was applied to the total number of patients in the asthma period alive that year. The year of diagnosis was included, but not the year of death. The expected numbers were then compared with the observed numbers, and expressed as a standardized ratio (SMR), and 95% confidence intervals were determined based on Poisson distributions.

This procedure was repeated for two subsets: cancer occurring within 5 yrs and after 5 yrs from the first treatment period of asthma, and also for each sex separately.

Results

Table 1 presents observed number of cancer cases, according to type, with SMRs and their 95% confidence intervals. For the total study population, a subdivision has been made by period of cancer development (during first 5 yrs after asthma diagnosis and later) and by sex.

Table 1 shows that the total number of cancers observed in men is 69% of the expected number, whilst in women the percentage is 62%. Thus, generally speaking, cancer rate is about 2 out of 3 of the expected rate.

Figure 1 shows a diagram comparing the expected number of cancers with the observed numbers for the various types. The dotted line in the diagram represents the 1:1 line, which would represent the situation of no effect of the asthma on cancer risk; the solid line represents the average cancer risk among the asthmatics (2 out of 3 of the population risk).

Table 1 – Observed (Obs) numbers of cancer with SMR (%) and its 95% confidence interval (95% CI) according to location

Diagnosis/location	Obs	SMR	95% CI
Lip-pharynx	84	60	48.8–74.6
Oesophagus	44	67	49.9–89.8
Stomach	188	50	43.0–56.9
Intestine	25	73	49.2–107.4
Colon	389	72	65.2–79.4
Rectum and anus	188	59	51.6–68.5
Liver, biliary duct	167	65	55.6–75.2
Pancreas	160	64	55.0–74.8
All respiratory tract	632	105	97.0–113.4
Breast	385	53	47.4–58.1
Uterine cervix	45	52	38.9–69.1
Uterine body	60	36	28.5–46.3
Uterine, unspecified	11	58	32.5–104.3
Ovarium *etc.*	91	52	42.1–63.1
Other female genital	14	49	29.3–81.8
Prostate	671	72	66.7–77.6
Testis	5	37	15.8–85.2
Other male genital	7	57	27.2–117.2
All urinary tract	390	67	60.4–73.6
Malignant melanoma	51	34	26.3–44.4
Skin	174	76	65.2–87.7
Eye and nervous system	154	75	63.9–87.6
Thyroid	25	47	31.7–68.1
Endocrine glands	100	96	79.3–117.3
Connective tissue and skeleton	25	46	31.1–67.2
Non-Hodgkin	104	61	50.6–74.0
Hodgkin	23	68	45.5–102.5
Multiple myeloma	39	38	28.3–51.8
Leukaemia	110	55	45.9–66.4
Other, unspecified	159	73	62.6–85.3
By period			
First 5 yrs	2433	67	64.3–69.6
After 5 yrs	2087	64	61.8–67.2
By sex			
Males	2641	69	66.1–71.4
Females	1879	62	59.3–64.8
Total	4520	65.7	63.9–67.7

SMR: standardized morbidity rate; 95% CI: 95% confidence interval.

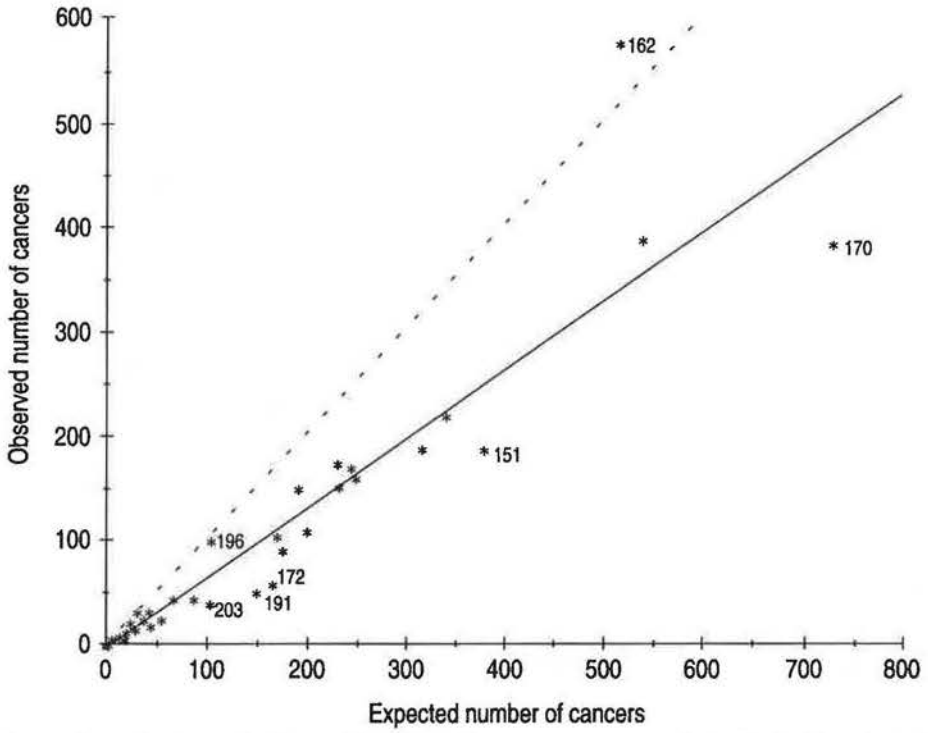

Fig. 1. – The diagram shows the observed and expected number of cancer cases, among patients who had been treated in hospital for asthma. The expected number was calculated from the population, with consideration of year of diagnosis, year of birth and sex of the patient. The dotted line corresponds to the 1:1 line, *i.e.* the observed and expected numbers are identical. The solid line corresponds to the average cancer rate in the group (2 out of 3 of that in the population). Each tumour is represented with an asterisk. Those deviating significantly from the unbroken line ($p<0.01$) are labelled with the ICD 7 code. 151: stomach cancer; 162: respiratory tract cancer; 170: mammary cancer; 172: uterine body cancer; 191: malignant melanoma; 196: cancer of endocrine glands; 203: multiple myeloma.

Table 1 and figure 1 show that respiratory tract cancer lies slightly above the 1:1 line, and cancer of endocrine glands very close to that line. A further analysis of the respiratory tract cancer cases shows that the excess in cancer rate refers mainly to the first period after the first known asthma diagnosis. For the first 5 yrs, SMR=129% (95% confidence interval (95% CI) 116.9–141.6), for the following years SMR=77% (95% CI 67.6–88.2). The high SMR observed for respiratory tract cancer in the first period suggests that some of these patients received a diagnosis of asthma as an initial sign of a pulmonary cancer. On the other hand, multiple myeloma, malignant melanoma, mammary cancer, uterine body cancer, and stomach cancer all lie, highly significantly ($p<0.001$), below the unbroken line.

Discussion

This is probably the largest study made on the possible relationship between asthma and cancer, and the protective effect previously demonstrated in several studies [2] is born out. The study is a registry study, and (especially for asthma diagnoses) relies on coded information given at the discharge of the patients. This is necessary, in order to obtain large numbers and to make it possible to study specific cancer types. It is probable, however, that some nonasthmatic patients have been erroneously included in the cohort, which would bias the observed/expected ratios towards unity. On the other hand, it seems very unlikely that the asthma diagnosis can be biased by the later appearance of a cancer. The only situation in which this may occur is for respiratory tract cancers, where initial signs may be misinterpreted as asthmatic.

The analysis is based on a follow-up of the patients with respect to survival. Some may have emigrated and developed cancer, and/or died abroad, and these were not identified. Emigration rate from the country is low (5 per 1,000 in 1973), but this phenomenon will give a small overestimate of the expected number of cancers in the cohort.

The question of a confounding effect of differential smoking habits cannot be solved in the present registry study. This confounder is especially strong for respiratory tract cancers but may also exist for other cancer forms. Previously published studies [2, 7] indicate that smoking habits do not explain the association between asthma and lung cancer. Other life-style factors may also confound the analysis.

Interestingly, the "protective" effect of asthma differs between different cancer types, a phenomenon not previously demonstrated as far as we know. It was more marked for some types (multiple myeloma, malignant melanoma, mammary cancer, uterine body cancer, stomach cancer) than for other types. We see no obvious explanation for these differences. The differential effect on cancers of different origin suggests, however, that the

"protective" effect has a biological background, and is not due to unidentified bias.

Various tentative explanations for the protective effect can be suggested, the most popular being that the immunological hyperreactivity characterizing a patient with asthma may increase immunological surveillance of cancer cells and, therefore, decrease the risk for manifest cancer [2].

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