Is herpes zoster a marker for occult or subsequent malignancy?

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ABSTRACT

Background
It has been suggested that herpes zoster may be a marker for occult malignancy.

Aim
To examine the emergence of a subsequent cancer diagnosis in patients with and without herpes zoster.

Design of study
Retrospective cohort study.

Setting
Results were based on the database of Intego, an ongoing Belgian general practice-based morbidity registry, covering 37 general practitioners and including about 311 000 patient years between the years 1994 and 2000.

Method
Survival analysis comparing the emergence of malignancy in patients with and without herpes zoster.

Results
The number of patients below the age of 65 years with herpes zoster, cancer or both was too low to draw any sensible conclusions. Above the age of 65 years we identified a significant increase of cancer emergence in the whole group and in females (hazard ratio = 2.65, 95% confidence interval = 1.43 to 4.90), but not in males. No difference could be identified in the first year after the herpes zoster infection.

Conclusion
Our results do not justify extensive testing for cancer in herpes zoster patients. The association we identified, however, leaves open a number of questions with respect to the physiopathology behind it.

Keywords
cohort studies; herpes zoster; neoplasm; survival analysis.

INTRODUCTION

For many years, both herpes zoster and an increased risk of malignancy have been associated with immune suppression. It has also been well documented that herpes zoster occurs more frequently in patients with a previously diagnosed malignancy.[1] Although suspected of being a predictor of malignancy or a marker of an occult malignancy, information on this subject is scarce. As well as a series of partly overlapping case-control studies, we only found two[2,3] cohort studies examining this topic. If it could be proven that herpes zoster is an indicator of occult cancer, this could alert GPs to signs and symptoms indicating possible malignancy, and screening patients for cancer might be considered. If it is a risk factor for the development of subsequent cancer, this could indicate the need for further research, both epidemiological and biological.

We examined the emergence of subsequent cancer in patients with and without herpes zoster, using the database of an ongoing general practice-based morbidity registry. We looked separately at cancers found during the first year after a herpes zoster episode to see if it can be considered to be a marker of the presence of an occult cancer.

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METHOD

Patients

Data was obtained from Intego, a general practice-based morbidity registration network in Belgium,[4] in the Department of General Practice at the Catholic University of Leuven. Thirty-seven GPs, who were registered using the medical software program Medidoc®, collaborated in the Intego project. These GPs worked in 34 practices evenly spread over Flanders, Belgium. GPs presented themselves for inclusion in the registry, but before their data were accepted, their registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with the best performance (from around 50% of the applicants) were included in the database. The Intego GPs prospectively registered all new diagnoses together with new drug prescriptions and laboratory results, using computer generated keywords linked to codes. The incidences of the diagnoses were classified according to a very detailed own classification as well as to ICPC-2 (International Classification of Primary Care),[5] a classification system for morbidity in general practice accepted and used worldwide.

Using specially framed extraction software, all new diagnoses were collected from the GPs' personal computers and entered into a central database. In early 2001 the database contained information about 82 000 different patients and over 311 000 patient years for the period 1994–2000. The database contains background information on patients' sex and year of birth. Registered data were continuously updated and historically accumulated for each patient. For this study, all diagnoses registered in the years 1994–2000 were used. From each diagnosis the date and the diagnostic code were registered.[4]

Diagnostic categories

Within the Intego network, no predefined criteria were used for entering a diagnosis. The registering GP used their own clinical skills and prescribed additional tests as considered appropriate. In complex medical conditions, or in the case of a patient directly consulting a specialist, the registration was based on specialist diagnoses that were systematically reported to the GP.

As the clinical picture was the only method of diagnosis of herpes zoster, and this was sufficient, this procedure did not present any problems. This was confirmed by our incidence rate (3.55 per 1000 patient years), which was within the range found in other studies (between 1.3 and 4.8 cases per 1000 person years) as reviewed by Helgason et al.[6] For a diagnosis of cancer, the situation is different. We therefore sent a questionnaire to all the registered

How this fits in

Previously, it was suggested that herpes zoster could be a marker of occult malignancy. This study shows that this is not the case. It also identifies herpes zoster as a predictor of subsequent malignancy.

GPs, listing the codes of a sample of their patients who were diagnosed with malignancy and asking them for the tests on which each diagnosis was based. For practical reasons, the sample included all patients with a previous episode of herpes zoster and a 50% random sample of all other cases. Thirteen patients could not be included by the GP. Based on this information, the diagnosis was confirmed histologically in 79%, at least cytologically in an additional 13%, and based on MRI (magnetic resonance imaging), CAT (computerised axial tomography) scan or endoscopy in 4%. Of the 10 remaining cases no information on method of diagnosis was available, but four of them were diagnosed during a hospital stay. We also compared the Intego incidence rate with the incidence rate of the local cancer registry.[7] In the Intego database the incidence rate of malignancy is 3.63 per 1000 patient years, which is comparable with the local cancer registration rate, and gave a crude incidence rate of 3.81 per 1000 person years.

Retrospective cohort study

Patients who had had a herpes zoster episode during the registration period (1 January 1994 to 31 December 2000), using the date of diagnosis as the baseline date, were included. Our control group consisted of all patients without a previous diagnosis of herpes zoster, who were of the same sex and born in the same years as the patients with herpes zoster.

Each time a herpes zoster patient was included in the study, all other patients from the same sex and the same year of birth as the index patient were included in the study population. The date of diagnosis of the index patient was assigned to the no-herpes zoster patients as a baseline date for the study. To prevent double use of control patients when more than one patient from the same sex and the same year of birth was diagnosed with herpes zoster, the different dates of diagnosis within each age–sex category were randomly assigned to all control patients from the same sex and the same birth year.

We excluded those who were diagnosed with malignancy before the assigned date of inclusion. Both groups of patients (with and without herpes zoster) were followed for an emerging first diagnosis

of malignancy. Follow-up of patients lasted until the end of the registration period, or earlier in the case of emergence of cancer.

Analysis

To compare the risk of malignancy in patients with and without herpes zoster, we used exploratory time-to-event techniques based on Kaplan–Meier survival curves[8] and log rank tests, as well as the more formal Cox proportional hazards model.[9] To that purpose, we defined an 'event' as diagnosis of a malignancy. Baseline was the date of diagnosis for the herpes zoster patients or the date of herpes zoster diagnosis of the index case for the matched set. Patients who did not develop malignancy during the study period were censored on the last day of the study period. As registration of death was not considered sufficiently reliable (most GPs do not consider it as a real diagnosis), it was not used for censoring.

The relationship between an episode of herpes zoster and the time to a diagnosis of malignancy was initially examined by the production of Kaplan–Meier curves, and tested using the two-tailed log rank test. The Cox proportional hazards model was applied to investigate this relationship more formally, while at the same time it enabled us to perform sex-stratified and age-adjusted analyses. To examine the proportional hazards assumption in the Cox regression model, a time-dependent variable was added to the model according to Collett.[10] A test of the hypothesis that this time-dependent variable has no effect is then a test of the assumption of proportional hazards.

The analyses were performed for the whole group as well as for subgroups of age and sex, if appropriate. Additional analyses considered only specific cancer sites.

Patients were split into three groups, representing patients aged 0–50 years, 51–65 years and over 65 years. SAS software was used for the statistical analyses.[11]

Ethical considerations

Before sending the data to the central database in Leuven, patient identification information is encrypted in each general practice using a one-way encryption algorithm. As a result, only the registering GP is able to find out to which patient a certain code belongs; for example, to provide additional information. Because of the large number of patients involved and because of the irreversibility of the algorithm, it is impossible to individually inform each patient concerned. According to the national privacy law, however, patients are informed about the registration through a poster on the wall in the waiting room of the registering GP.

RESULTS

Patient characteristics

The analysis includes 80 028 patients with no evidence of malignancy at the date of inclusion in the cohort, of whom 1211 patients developed herpes zoster in the period 1994–2000, and 78 817 patients did not develop it in the same period.

The demographic characteristics of these patients are listed in Table 1. Males and females were about equally distributed among patients with and without herpes zoster. Patients aged 50 years or less were more frequent than older patients in both cases and controls.

Exploratory analysis

A subsequent malignancy was diagnosed during the study period in 609 subjects. Of these cases, 25 had herpes zoster. Follow-up time ranged from 3–2553 days among patients who had herpes zoster and from 5–2552 days among patients who did not have herpes zoster diagnosed at the start of the study (Table 1).

Table 2 shows summary statistics for the duration between diagnosis of herpes zoster and cancer diagnosis in general, and for several specific cancer sites. Since time to malignancy is a censored variable, we used the median instead of the mean to describe the follow-up period.[10] In general, it is striking that the standard deviations (SDs) were large, indicating the absence of a specific period after which the causal influence of herpes zoster on cancer would become apparent.

Kaplan–Meier estimates of the time-to-event functions show a difference between the two groups of herpes zoster patients in relation to emergence of malignancy (log rank = $P<0.0001$ for females and $P = 0.0002$ for males), with more cancer cases after herpes zoster infection. A strong interaction was found with age.

In female patients aged 65 years or less, there were only two events in the case group, which is not really informative due to lack of power. In female patients who were aged more than 65 years, there was an increasing difference between cases of herpes zoster and patients without herpes zoster in relation to time to emergence of malignancy (Figure 1). For this cohort of patients, at any given time, the estimated percentage without malignancy was higher for patients without herpes zoster. The log rank test for this cohort ($P = 0.001$) supported a significant difference.

For males, the number of events in herpes zoster patients was very low for those aged below 65 years (three events). In males aged over 65 years, the time-to-event curve for cases lay completely below that of patients without herpes zoster (Figure 2). However, using a formal log rank test we were not able to

establish a significant difference (P = 0.36).

We repeated the previous analyses for males and females combined. Figure 3 represents the unstratified and age stratified time-to-event curves. From this figure there was clearly a significant difference between cases and no-herpes zoster patients aged above 65 years with respect to their time-to-event curves. This difference is confirmed by the log rank test, which yields a P-value of 0.004.

Cox regression analysis

After adjustment for age, the hazard ratio (HR) for female patients older than 65 years was 2.65 (95% confidence interval [CI] = 1.43 to 4.90). For male patients in the same age group the HR is only 1.37 (95% CI = 0.70 to 2.67). For males and females above the age of 65 years combined, the sex-adjusted HR = 1.85 (95% CI = 1.18 to 2.90).

First year only analysis

In addition, we investigated the effect of herpes zoster infection on diagnosis of malignancy within the first year of follow-up. An age and sex adjusted analysis based on the group of males and females combined yielded no significant relationship (HR = 1.75, 95% CI = 0.82 to 3.75). This was confirmed in each of the six age and sex stratified subgroups when analysing them separately.

Analysis of cancer subgroups according to site

Table 3 shows the age-adjusted HRs for herpes zoster versus no-herpes zoster patients in relation to the emergence of the main subgroups of malignancy according to their primary site. A borderline statistically significant result was found for female colorectal cancer only, potentially indicating that female cases are more likely to have a subsequent diagnosis of colorectal cancer than those without herpes zoster. The time between herpes zoster and cancer diagnosis in female colorectal cancer patients ranged from 352–892 days.

DISCUSSION

Summary of main findings and relationship with the existing literature

Our results indicate a relationship between the presence of herpes zoster and the risk of a subsequent cancer diagnosis in patients over the age of 65 years. No relationship could be identified in younger patients. However, even if such a relationship does exist, it would be difficult to prove due to the low number of patients with herpes zoster and cancer in these age groups, even in very large cohorts. In this study, diagnosed patients tended to be older than control patients. However, our results were controlled for age by adding age as a co-variable or by stratifying by age.

**Table 1. Descriptive characteristics of the study population.**

	Patients with herpes zoster n = 1211	Patients without herpes zoster n = 78817
Number of patients with malignancy (%)	25 (2.06)	584 (0.74)
Range of follow-up (days)	3–2553	5–2552
Mean age in years at baseline (SD)	47.4 (23.4)	36.6 (21.3)
Sex (n [%])		
Male	551 (45.50)	38859 (49.30)
Female	660 (54.50)	39958 (50.70)
Age group at baseline in years (n [%])		
0–50	607 (50.12)	58538 (74.27)
51–65	275 (22.71)	11013 (13.97)
>65	329 (27.17)	9266 (11.76)

SD = standard deviation.

Table 2. Time in days from herpes zoster to cancer diagnosis.

Type of cancer	Median time in days (SD)
All types of cancers combined	572 (400)
Lung	485 (188)
Prostate	574 (518)
Breast	693 (331)
Colorectal	371 (336)

SD = standard deviation.
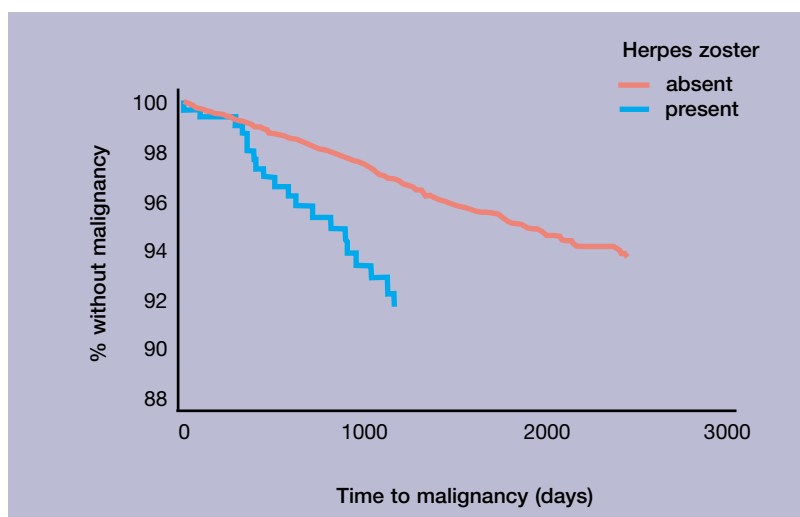
Figure 1. Estimated curves of the proportion without malignancy for patients aged over 65 years with or without herpes zoster, males and females combined.

As an association between herpes zoster and cancer diagnosis was not found during the first year of follow-up, the results do not support the role of herpes zoster as an indicator or marker of an undiagnosed malignancy as suggested since 1955[12] and until recently.[1,13] This finding has been confirmed by other studies.[3,14]

The association in subsequent years has so far not been described in cohort studies. This may be because only two previous cohort studies have
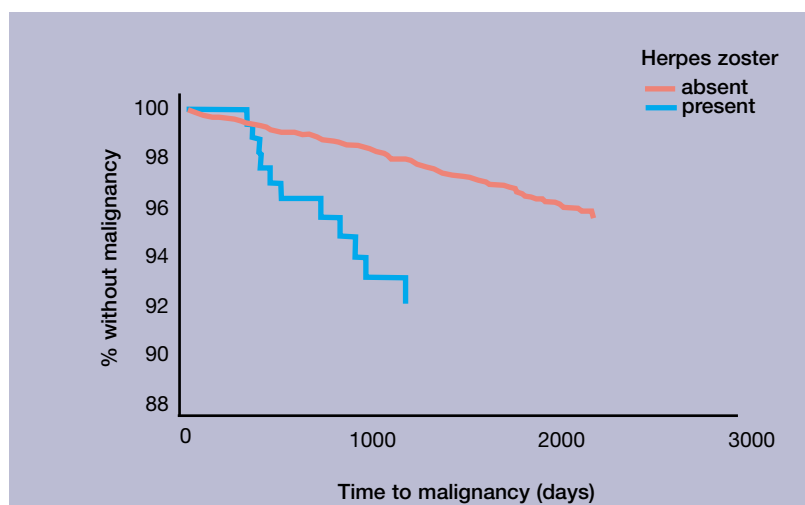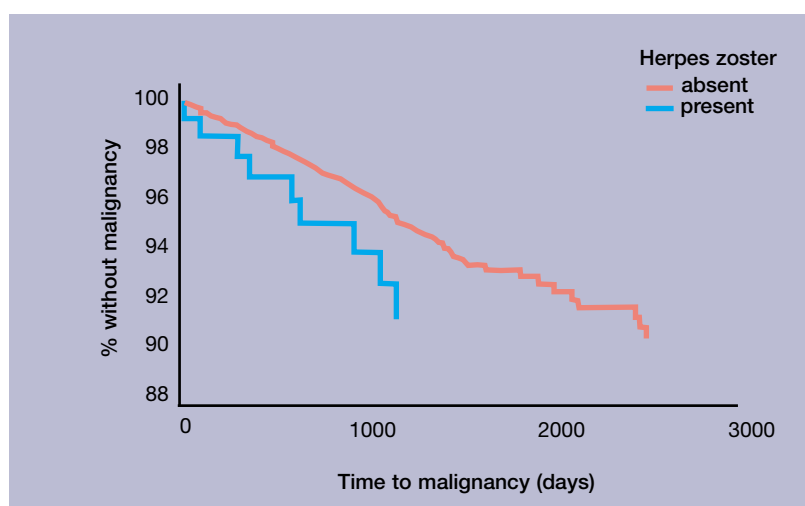
Figure 2. Estimated curves of the proportion without malignancy for female patients aged over 65 years with or without herpes zoster.

only. The absence of statistical significance in males may indicate a weaker or absent relationship between herpes zoster and subsequent cancer emergence in males or it may result from insufficient power.

Strengths and limitations of this study

Any study investigating an increased incidence of one disease conditional on the diagnosis of another disease in a clinical setting may suffer from indication bias. In our study, it is unlikely that this is a strong factor as herpes zoster is an acute disorder with a relatively short duration, and the increased emergence of malignancy was not more in evidence during the first year following the diagnosis of herpes zoster.

examined it, one of which included only two groups of 50 patients.[2] Ragozzin *et al*[3] did not find any relationship after comparing the cancer risk of 590 herpes zoster patients with the rates expected on the basis of the local cancer registry data in Rochester, US. There have been no studies in which a group of elderly patients has been separately analysed. In our study the relation was found to be statistically significant for all patients above the age of 65 years, and, after stratifying for sex, for females

Implications for future research and clinical practice

The association between herpes zoster and subsequent malignancy in a cohort study suggests that herpes zoster precedes the appearance of the malignancy. In our view, this can be explained by three mechanisms. Firstly, as some cancers — especially haematological cancers — are known to be present in a pre-clinical and undetectable form for 10 years or more before diagnosis,[15-17] the herpes zoster could be an early manifestation of the impairment of the immune system provoked by the malignancy.

Alternatively, it is possible that herpes zoster virus triggers some immunological mechanism; for example, virus particles may provoke an antigenic stimulation or change a tissue antigen, leading to the development of malignancy. Such reasoning is also supported by the finding of different types of malignancies (lymphoma, pseudolymphoma, angiosarcoma, Kaposi's sarcoma) at the same site as a previous herpes zoster infection.[18,19]

Finally, both reactivation of the virus and immunological surveillance against malignancy[20,21] are related to cellular immunity (CD4+ T cells and natural killer cells). Any dysfunction of such a mechanism can therefore result in the emergence of

Figure 3. Estimated curves of the proportion without malignancy for male patients aged over 65 years with or without herpes zoster.

Table 3. Estimated hazard ratios according to site of cancer.

| Cancer site | Males | | Females | |
	n	Hazard ratios (95% CI)	*n*	Hazard ratios (95% CI)
Lung	51	1.225 (0.297 to 5.060)	a	
Prostate	53	1.903 (0.589 to 6.143)	a	
Breast	a		81	2.765 (0.970 to 7.884)
Colorectal	26	1.530 (0.204 to 11.451)	22	4.001 (1.123 to 14.257)
Haematological	72	1.864 (0.676 to 5.140)	60	1.314 (0.311 to 5.544)

CI = confidence interval. [a]Fewer than 20 cases.

both herpes zoster and malignancy. In some cases herpes zoster would emerge first and in other cases malignancy.

In summary, our study results do not justify extensive testing for cancer in patients with herpes zoster. However, the association we have identified leaves a number of questions open with respect to the physiopathology behind it, especially the question why not all herpes zoster patients get cancer and vice versa.

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