

# Bowen Disease and Risk of Subsequent Malignant Neoplasms

## A Population-Based Cohort Study of 1147 Patients

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**Objective:** To address the long-standing question of whether patients with Bowen disease are at increased risk of internal malignant neoplasms.

**Patients:** A total of 1147 Danish patients diagnosed between 1978 and 1993 as having Bowen disease at nongenital sites were followed up for 6463 person-years for cancer occurrence up to 16 years after the skin lesion.

**Main Outcome Measure:** Standardized incidence ratios (SIRs)—the ratios of observed-to-expected numbers of cancer—served as measures of relative risk.

**Results:** The observed number of noncutaneous can-

cers occurring in the cohort (n = 115) was close to expected (n = 103.0) (SIR = 1.1; 95% confidence interval, [CI], 0.9-1.3). However, nonmelanoma skin cancer (SIR = 4.3; 95% CI, 3.5-5.4; n = 83), lip cancer (SIR = 8.2; 95% CI, 2.6-19.1; n = 5), and, among men, leukemia (SIR = 3.2; 95% CI, 1.04-7.5; n = 5) occurred in excess.

**Conclusions:** Patients with Bowen disease do not appear to constitutionally be at any unusually high general cancer risk. The increased risk of invasive skin and lip cancers is likely due to the common risk factor of UV light.

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**F**OLLOWING A 1959 report by Graham and Helwig,<sup>1</sup> which suggested an association between Bowen disease (squamous intraepidermal neoplasia) and noncutaneous malignant neoplasms, several studies<sup>2-5</sup> were conducted before 1980 that confirmed this finding and another<sup>6</sup> that did not. Arbesman and Ransohoff<sup>7</sup> later criticized studies completed before 1983 for having methodologic flaws and concluded that the published clinical data did not provide convincing evidence of an association between Bowen disease and subsequent internal malignant neoplasms. The largest study to date was a Danish hospital-based study<sup>8</sup> of 581 patients diagnosed from 1943 to 1982 as having Bowen disease and followed up for occurrence of subsequent cancer. No significant excess risk of internal cancer was found among these patients (50 cancers observed, 40 cancers expected; standardized incidence ratio [SIR] = 1.3; 95% confidence interval [CI], 0.9-1.6).

To our knowledge, only 2 small population-based cohort studies have been performed. In Northern Ireland, 157 patients with Bowen disease diagnosed from 1970 to 1983 were followed up for the occur-

rence of subsequent internal malignant neoplasms.<sup>9</sup> A significantly increased cancer risk was found for men but not for women. However, the size of risk and the particular cancer types that occurred in excess were not presented, and the quality of the data used was later questioned.<sup>10</sup> In another study<sup>11</sup> in Rochester, Minn, all 71 patients with Bowen disease diagnosed between 1976 and 1984 were followed up for internal malignant neoplasms, and observed cancer rates were compared with the incidence in the population. Overall, no excess risk was found (SIR = 1.1; 95% CI, 0.4-2.5), but the numbers were small.

Based on figures from the Danish Cancer Registry (DCR), we present results of a population-based cohort study of 1147 patients diagnosed as having Bowen disease between 1978 and 1993 who were followed up for the occurrence of subsequent malignant neoplasms.

## RESULTS

We followed up 444 men for 2463 person-years and 703 women for 4000 person-years (median, 4.7 years for both sexes). Selected characteristics of the study cohort are presented in **Table 1**.

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## MATERIALS AND METHODS

The registration of incident cases of invasive cancers in the DCR is considered to be of high quality and close to complete.<sup>12</sup> All physicians in Denmark, whether in hospital or outpatient settings, must report each incident case of cancer, including skin cancer, to the DCR. Although notification of noninvasive skin cancers is not compulsory, incident cases of Bowen disease that are reported to the DCR are recorded in a manner similar to invasive cancers. For the purpose of this historical cohort study, patients with histologically verified tumors registered with topography codes 1731 to 1739 (skin exclusive of lip and external genitals) and histology code 80812 (Bowen disease) for the incidence years 1978 to 1993 were identified in the DCR. Patients who added no risk time to the analyses because of diagnosis at autopsy, death before the end of the month of diagnosis, or age at diagnosis older than 100 years were excluded from the cohort, as were those registered with cancers antedating their diagnosis of Bowen disease. The remaining 1147 patients (median age, 73 years; range, 20-99 years) were followed up for the occurrence of subsequent cancers from the month following the date of diagnosis until 100 years of age, death, emigration or December 31, 1993, whichever came first. Information about the end of follow-up was obtained through a link with the Civil Registration System, which keeps a continuously updated file on demographic variables (including death and emigration) for all citizens in Denmark. Sex-, age-, and period-specific patient-years of observation in the cohort (in 5-year blocks) were multiplied by their corresponding national rates of incidence to determine the expected number of cases of cancer in the cohort.

Stratified analyses were performed to evaluate cancer risk according to anatomic site of Bowen disease (sun-exposed sites: head, face, neck, or upper extremities; sun-protected sites: trunk or lower extremities), age at diagnosis of Bowen disease (<60 years or ≥60 years), and time since Bowen disease (<5 years or ≥5 years). The SIRs, serving as measures of relative risk, were calculated as ratios of observed-to-expected numbers of cancer. Assuming a Poisson distribution of observed cancer events, 95% CIs were calculated using Byar approximation.<sup>13</sup>

Overall, 201 subsequent cancers were observed among patients with Bowen disease; only 124.0 were expected (SIR = 1.6; 95% CI, 1.4-1.9) (**Table 2**). Among men, 109 subsequent cancers were observed (SIR = 1.9; 95% CI, 1.5-2.3); among women, 92 cancers were observed (SIR = 1.4; 95% CI, 1.1-1.7). A significant excess of certain cancers was observed: 83 cases of nonmelanoma skin cancer with only 19.1 expected (SIR = 4.3); 5 cases of lip cancer with only 0.6 expected (SIR = 8.2); and, among men, 5 cases of leukemia with only 1.6 expected (SIR = 3.2) (Table 2). When excluding subsequent melanoma and nonmelanoma skin cancers from the analyses, 64 cancers were observed among men (SIR = 1.3; 95% CI, 1.01-1.7); 51 among women (SIR = 0.9; 95% CI, 0.7-1.2). The excess of non-

**Table 1. Distribution of Bowen Disease of the Skin in 1147 Danish Patients, 1978-1993**

Characteristics	Patients, No. (%)	Patient-Years
Male	444 (39)	2463
Female	703 (61)	4000
Age at diagnosis, y		
<50	75 (7)	505
50-59	106 (9)	836
60-69	278 (24)	1849
70-79	357 (31)	2038
≥80	331 (29)	1236
Site of Bowen disease		
Face, head, and neck	461 (40)	2671
Trunk	162 (14)	889
Upper extremity	218 (19)	1250
Lower extremity	198 (17)	1038
Multiple sites*	81 (7)	464
Not specified	27 (2)	151

\*Patients with multiple Bowen disease lesions (synchronous or metachronous) were followed up from the month following first diagnosis.

cutaneous cancer among men was partly due to smoking-related cancers. Consequently, when subsequent lip and lung cancers were excluded, the SIR for noncutaneous cancer among men was 1.2 (95% CI, 0.9-1.6).

Selected cancers that occurred in excess are shown in **Table 3**. Men with Bowen disease on sun-protected sites were at elevated risk of developing internal malignant neoplasms: 19 noncutaneous cancers were observed; only 9.5 were expected (SIR = 2.0). Of those 19 cancers, 7 were lung cancers (SIR = 3.7). In contrast, men with Bowen disease on sun-exposed sites were not at significantly increased risk of internal cancer (SIR = 1.2) (Table 3).

Patients diagnosed as having Bowen disease before age 60 years, particularly men, appeared to be at higher risk of nonmelanoma skin cancer than those diagnosed as having Bowen disease at an older age (Table 3). Also, an excess of lung cancer was restricted to men diagnosed as having Bowen disease before age 60 years (SIR = 4.6; n = 5). All cases of leukemia occurred in patients diagnosed as having Bowen disease after age 60 years.

Occurrence of cancer did not seem to be restricted to any particular period, although the excess risk of leukemia in men was confined to the 5-year period immediately following diagnosis of Bowen disease.

## COMMENT

This cohort study, confirmed the excess risk of nonmelanoma skin cancer among patients with Bowen disease.<sup>5</sup> However, we found no strong association between Bowen disease and risk of subsequent internal malignant neoplasms in general, an observation that lends statistical support to suggestions from smaller studies.<sup>6,8,11,14</sup>

Peterka et al<sup>3</sup> reported considerably more internal cancers in patients with Bowen disease at anatomic sites considered to be sun protected than in patients with such skin lesions on sun-exposed skin. However, subsequent studies,<sup>5,6,8,11,14</sup> most of which had low statistical power, could not replicate this finding. We observed a 2-fold in-

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