A Link between Malignant Melanoma and Cervical Intra-epithelial Neoplasia?

A Preliminary Report

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The risk of malignant melanoma was found to be six times as great in a group of 805 patients with cervical dysplasia as in case-matched controls. In the latter it was similar to that in the general population. In keeping with this observation a further series of 13 030 women with no record of cervical intra-epithelial neoplasia showed a slightly lower risk than that expected in the general population. Conversely in a small group of women (71) with melanoma the risk of cervical intra-epithelial neoplasia was nine times as great as in the general population; judged on the basis of both case-matched and 'first smear' controls. The possibility of a common risk factor is discussed. (Received August 6, 1987.)

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Skin lesions of various types, including malignant melanoma, have been shown to occur with greater frequency in women with cervical dysplasia than in case-matched controls (1). This observation, which is new, give rise to concern as malignant melanoma is increasing sharply in our population (Table I).

We therefore set up a preliminary study, seeking more information on the observation. We have used material at present available, both retrospectively and in the form of two short-term prospective studies. The findings stress the need for definitive epidemiological evaluation of material from this and other districts.

PATIENTS AND METHODS

The Gade Institute provides the cytological and histopathological service for the county of Hordaland, Norway and surrounding district, and regularly reports all malignancies to the Cancer Registry. Cervical dysplasia is not recorded by the Registry.

Malignant melanoma in patients with/without cervical dysplasia

The observation of a possibly increased incidence of malignant melanoma in patients with cervical dysplasia was made in 805 cases presenting here in the first half of 1984, for which case-matched controls had been selected. As reported previously (1), in each case the next woman born in the same year who presented for gynaecological cytology subsequent to the first investigation in the test case, was used as a control. These cases were thus also matched for the number of years they had been on our cytology files. The number of woman-years involved here was now calculated. The histology files were searched for records of malignant melanoma from these cases between 1981 and 1984 inclusive.

Next we collected the records from all women presenting for a cervical smear in the first 6 months of 1986 in whom there was no record of cervical intra-epithelial neoplasia (CIN). There were 13 030 of them. Again the histology files were searched for records of malignant melanoma in them between 1981 and 1984.

Cervical intra-epithelial neoplasia (CIN) in patients with/without malignant melanoma

There were 71 women on our files in whom a primary cutaneous melanoma had been diagnosed between 1981 and 1984 and for whom cervical cytology was available. These 71 cases were matched with controls, i.e. the first woman born in the same year presenting for gynaecological cytology

subsequent to the first cytological specimen in the test case. These controls had thus the same number of years at risk for the development of a cervical lesion, as both were on our files from the start of the period. During this time only 2 of the controls did not have a repeat smear (mean number of smears (±SD): 3.0±2.7). In the test cases the mean number of smears was 3.2±3.2. This difference vis-à-vis the controls is not statistically significant.

The records for the first 300 women presenting here for routine gynaecological cytology for the first time in 1986 were also collected as the incidence of CIN has not been reported in our material. Their age was noted and also the number of cases with CIN. (Five cases were rejected as the smear did not contain representative material.)

RESULTS

Malignant melanoma

The incidence of invasive melanoma has increased from 9 to 15/100 000 in women in Hordaland over the past decade (Table I). Using 15/100 000 as the basis for calculation, the presence of 3 invasive malignant melanomas per 3 542 woman-years (1 : 1 175) in patients showing cervical dysplasia is approximately six times the expected figure (1 : 6 666). No corresponding case of melanoma was found in the 805 case-matched controls, in keeping with the expected rate in women in the population as a whole.

Table I. *Malignant melanoma in women from the county of Hordaland, Norway in 1972–76 and 1981–83 giving the crude incidence per 100 000*

	Malignant melanoma in women in Hordaland (invasive)		
Year	No. of cases[a]	Population (female)[a]	Crude incidence per 100 000
1972–76	88	194 462[b]	9.05[c]
1981	22	197 907	11.12
1982	25	198 640	12.59
1983	30	199 420	15.04

[a] Refs. 7–10.
[b] 1974.
[c] Age-adjusted, 9.8 (7).

Table II. *Age distribution of the cases of malignant melanoma in women with/without cervical intra-epithelial neoplasia (CIN), see text*

Group	Age (yrs) at time of study							
Women with melanoma	85	75	65	55	45	35	25	All
With benign gyn. cytology	3	2	15	15	14	9	4	62
With CIN			1	3	1	2	2	9
Total	3	2	16	18	15	11	6	71
First smear controls								
With benign gyn.cytology			26	21	26	48	126	286
With CIN			1	1	2	2	3	9
Total			27	22	28	50	129	295

Five invasive melanomas had occurred over the same 4-year period in the 13030 women with no record of CIN. This gives a rate of 1:10424 woman-years, which is lower than expected.

CIN was found in 9 of the 71 patients with malignant melanoma (Table II), all of whom were under 65 years of age. Details of the lesions are given in Table III. In the 71 case-matched controls one patient was found with cervical dysplasia in one smear. None had malignant melanoma.

These cervical lesions were thus nine times as common in our patients with melanoma as in these controls.

The further control group presenting for their first smear naturally contained more younger women than the test group and its case-matched controls (Table II). Cervical dysplasia was seen in 8 cases, 'in situ' carcinoma in one. The corresponding figures for the patients with malignant melanoma were 9 of 71. This difference is statistically significant (χ^2 with Yates' correction = 9.4, $p<0.005$). The numbers are low, but the contrast—particularly in the two younger age groups—is marked. Here, CIN was found in 4 of 17 cases of malignant melanoma compared with 5 of 179 controls; i.e. 8.4 times as often.

DISCUSSION

In the present study we demonstrate an increased risk of malignant melanoma in patients with cervical dysplasia. The risk in women with dysplasia was 6 times that in 805 case-matched controls and 9 times greater than that in the sample of 13030 women without record of CIN. In the latter it was marginally lower than expected, in keeping with the finding of an excess in women with dysplasia. These findings are preliminary and must be viewed with caution. Malignant melanoma is however a serious disease. The present data thus indicate a need for prospective epidemiological studies.

In addition we have shown that the reverse also applies. Nine cases of CIN occurred in 71 patients with malignant melanoma, while one was found in controls without melanoma matched with the cases with regard to the length of time they had been under gynaecological surveillance. 'First smear' controls from the same population showed a similar difference, i.e. a nine-fold greater risk of CIN in patients with melanoma. Here again the evidence is limited, stressing the need for further data.

There is little to be found in the literature regarding any relationship between malignant melanoma and cervical neoplasia. A survey from Denmark (1943–80) showed a slight

Table III. *Details of the 9 cases of malignant melanoma in which a neoplastic lesion of the uterine cervix was also present, see text*

Cervical lesion		Malignant melanoma	
Type	Year	Year	Type
Dysplasia	1975	1983	Nodular
Dysplasia	1975	1984	Sup. spread (inf.)
Dysplasia	1975	1984	Sup. spread
Dysplasia	1981	1982	Sup. spread ("in situ")
Ca. "in situ"	1981	1981	Nodular
Ca. "in situ"	1984	1984	Sup. spread (inf.)
Dysplasia	1984	1984	Nodular
Dysplasia	1985	1982	Sup. spread (inf.)
Dysplasia	1985	1982	Sup. spread (inf.)

increase in invasive carcinoma of the uterine cervix within a year of diagnosis of malignant melanoma (2). This however was not seen in a corresponding study from USA (3). As cervical dysplasia is an eminently treatable condition, lack of increase in infiltrative cervical cancer is no evidence of lack of connection with dysplasia. Further, in an international study it was shown that women with 'in situ' cervical carcinoma do not have an increased risk of developing malignant melanoma. This massive data was however collected between 1960 and 1970 (4), a period during which the incidence of malignant melanoma was much lower than it is now. This conflicting evidence again stresses the need for further study.

The nature of the implied link between malignant melanoma and cervical dysplasia is not known. One report, however, is of interest here in view of the known association between melanoma and exposure to ultraviolet light (5). That is the observation that the skin lesions in the rare condition epidermodysplasia verruciformis which, like cervical neoplasia, is associated with the human papilloma virus, only develop following exposure to ultraviolet light (6). This possible link with human papilloma virus is under investigation in the present material. It suggests that exposure to sunlight alone may not be responsible for the increase in melanoma seen in both sexes in recent years.

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