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Condylomata acuminata and risk of cancer: an epidemiological study

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Abstract

Objective—To determine whether patients with condylomata acuminata have an increased risk of developing cancer.

Design—Prospective cohort study on patients diagnosed as having condylomata acuminata. The number of malignant tumours in the cohort was compared with national incidences obtained from the Swedish Cancer Registry.

Setting—Dermatology department of the Karolinska Hospital, Stockholm, Sweden.

Subjects—3260 patients (2549 males and 711 females, median (range) age 23 (1-80) years) seen during 1969-84, with a mean follow up of 7.8 years.

Main outcome measures—Number of malignant tumours observed in the cohort during the study period and expected number from national incidence.

Results—There were 27 malignancies in the study group. There was no significant increase genital cancer in females compared with the national incidence. Only one patient had invasive cervical cancer (relative risk=1.8; 95% confidence interval 0 to 10.1). Seventeen women had cervical carcinoma in situ (1.5; 0.9 to 2.5) compared with an expected number of 11.5; this increase was not significant. For males 22 cancers were observed at all sites (1.6; 1.0 to 2.5). The number of genitourinary cancers observed in males was almost three times higher than expected (2.6; 1.2 to 5.0).

Conclusion—The results indicate that the risk of developing cervical carcinoma in situ or invasive cervical cancer after a genital human papillomavirus infection is less than previously thought. The implications of increase in the genitourinary malignancies in males are uncertain.

Introduction

Condylomata acuminata and cancer are ancient diseases.¹ The first descriptions of condyloma were given by ancient Roman physicians.² It was realised early on that condyloma was a venereal disease, and it has been connected with syphilis and, later, homosexuality.³ It was not until 1954 that the true nature of transmission was elucidated. American soldiers in Korea developed condyloma after having sexual intercourse with indigenous women. Four to six weeks after

their homecoming their wives developed condyloma.⁴ The viral aetiology was established in 1968, when viral particles were identified in genital warts,⁵ and 10 years ago it was found that the particles were strains of human papillomavirus other than the strain that causes verruca vulgaris.⁶ Today more than 60 types of the virus are known, some of which have several subtypes.⁷ The clinical importance of some of these types is not clear. Human papillomavirus types 6 and 11 are associated with benign condylomatous lesions and low grade cervical intraepithelial neoplasia, and human papillomavirus types 16 and 18 are associated with cervical intraepithelial neoplasia and invasive cancer.⁷

The association between genitoanal human papillomavirus infection and cancer is not new. There are several reports of patients with coexistence of condyloma and malignant neoplasm or cervical intraepithelial neoplasia.⁸⁻¹¹ Human papillomavirus structural proteins have been found in patients with cervical intraepithelial neoplasia.¹²⁻¹³ DNA hybridisation has shown human papillomavirus types 16 and 18 DNA sequences in lesions of invasive cervical cancer, integrated in the genome of the malignant cells.¹⁴

Although it is now becoming increasingly accepted that some human papillomavirus types are involved in the induction of genital cancers there is no clear epidemiological evidence that they cause cancer.¹⁵ We know of only one large prospective study on the development of malignancy in patients with condyloma,^{16,17} though numerous papers report the recent increase in the incidence of condylomata acuminata.^{16,18} In this study we investigated the development of genital cancer in a large group of patients with condyloma.

Patients and methods

Patients—During 1969-84, 3260 patients with condylomata acuminata were seen at the dermatology department of our hospital. We examined the patients' records and recorded the year of diagnosis, age, and sex. The records of patients seen during 1974 and 1975 were not available. The patient population consisted of 2549 males and 711 females (fig 1), with a median (range) age at diagnosis of 23 (1-80) years. The mean follow up period was 7.8 years. The number of person

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FIG 1—Age distribution of 3260 patients with condyloma

years of observation was calculated separately for each sex and amounted to 20 104 for males and 5603 for females.

Swedish Cancer Registry—Information from the Swedish Cancer Registry in Stockholm for 1958-84 on the 3260 patients was correlated to identify people with malignant tumours. Nationwide information on the incidence of cancer in Sweden is available from 1958, when compulsory registration began.¹⁹ For classification of the cancers the seventh revision of the International Classification of Diseases was used. The registry collects information on patients with cancer from both clinicians and pathologists.¹⁹ Thus most cases are notified with two reports.¹⁹ If a patient has more than one primary tumour each tumour is registered separately. Each patient's identification number, which is used in all population statistics in Sweden, is composed of six digits based on year, month, and day of birth, supplemented with a registration number (three digits) and a check digit. The identification number is not affected by changes in names. The completeness of registration is close to 100% for all cancers.²⁰

Statistics—The length of follow up was calculated for each patient. This was the time from diagnosis of condyloma until 1985, the last year on line at the cancer registry at the time of the study. The expected number of malignant tumours was estimated on the basis of length of follow up and data on national incidence¹⁹ and prevalence²¹ of cancers from the registry with a computer program developed specifically for this purpose.²² The estimate for each patient was calculated by using the age and calendar specific national incidence and deducting the probability of death in that age group for each year the patient was in the study. Finally, the individual probabilities were summed.

This method has been described in detail elsewhere.²² Regional differences were ignored.

After the ratio between the observed and expected number of malignancies had been estimated, significance and confidence analysis was performed, assuming the variable to have a Poisson distribution. All other statistics and tabulations were done with the SPSS statistical package under the OS/2 operating system.

Results

Among the 3260 patients with condyloma, 27 malignancies were diagnosed at the same time as or after condyloma was diagnosed (table I). On the basis of the Swedish national incidence data 2549 males and 711 females in the general population would be expected to have 13.4 and 5.6 malignancies respectively. As compared with morbidity in the general population, the morbidity due to cancer produced a relative risk of 1.6 (95% confidence interval 1.0 to 2.5) for males and 0.9 (0.2 to 2.1) for females. Only 0.6 invasive cervical cancers were expected in the patient group, but one case was observed (relative risk 1.8; 95% confidence interval 0 to 10.1). Nine genitourinary cancers were observed in males, but only 3.4 were expected (2.6; 1.2 to 5.0). Table II gives the characteristics of the genitourinary tumours in males and the time interval to diagnosis after diagnosis of condyloma. Cervical carcinoma in situ was analysed separately; there were 17 cases, but only 11.5 were expected (1.5; 0.9 to 2.5).

To investigate further the risk of genitourinary cancer the material was stratified according to length of follow up. A total of 915 (28%) patients were followed up for one to four years, 1351 (41%) for five to nine years, and 994 (30%) for more than 10 years. Table III gives the relative risks.

Discussion

The first epidemiological reports of a possible association between condyloma and cancer go back to 1953, when four cases of vulvar cancer preceded by a condyloma infection were described. Since then more than 60 cases of genital cancer in association with condyloma have been reported.²³ Since the development of the DNA hybridisation technique many workers have reported an association between human papillomavirus infection and cervical carcinoma. Human papillomavirus types 16 and 18 are found in up to 90% of patients with cervical carcinoma,²⁴ and it is not known if the remaining 10% really are negative for the virus. It has also been shown that up to a half of

TABLE I—Observed and expected numbers of malignancies among 3260 patients with condyloma*

Site of cancer†	ICD 7 code	Males				Females			
		Expected	Observed	Relative risk	95% Confidence interval	Expected	Observed	Relative risk	95% Confidence interval
All sites	140-210	13.4	22	1.6	1.0 to 2.5	5.6	5	0.9	0.2 to 2.1
Gastrointestinal tract	140-158	2.7	5	1.8	0.6 to 4.3	0.8	0	0	0 to 3.7
Respiratory system	160-164	1.2	2	1.7	0.2 to 6.2	0.2	1	6.3	0.1 to 34.8
Trachea, bronchus, and lung	162	1.0	2	2.1	0.3 to 7.6	0.1	0	0	0 to 3.7
Breast	170					1.4	2	1.4	0.2 to 5.2
Genitourinary organs in females	171-176					1.3	1	0.8	0 to 4.3
Cervix	171					0.6	1	1.8	0 to 10.1
Genitourinary organs in males	177-181	3.4	9	2.6	1.2 to 5.0				
Testes	178	1.4	4	2.1	0.8 to 7.2				
Urinary organs excluding kidney	181	0.7	2	3.0	0.4 to 10.9	0.1	0	0	0 to 3.7
Skin	190-191	1.4	0	0	0 to 3.7	0.5	0	0	0 to 3.7
Central nervous system	192-193	1.2	1	0.8	0 to 4.5	0.3	1	2.9	0.1 to 16.4
Other sites	199	0.3	2	6.3	0.8 to 22.6	0.1	0	0	0 to 3.7
Blood and blood forming organs	200-210	2.0	3	1.5	0.5 to 5.1	0.4	0	0	0 to 3.7
Malignant lymphoma	200	0.6	2	3.4	0.4 to 12.2	0.1	0	0	0 to 3.7
Cervical carcinoma in situ	171					11.5	17	1.5	0.9 to 2.5

ICD 7=Seventh revision of the International Classification of Diseases.

*Includes malignancies diagnosed at the same time as or after condyloma was diagnosed.

†All sites with two or more cases for either sex.

TABLE II—Characteristics of genitourinary tumours in males*

Site of cancer	ICD 7 code	Histological type	Time after diagnosis of condyloma (years)	Age at diagnosis of condyloma (years)
Prostate	177	Adenocarcinoma	-2	71
Prostate	177	Adenocarcinoma	5	58
Testis	178	Seminoma	5	33
Testis	178	Embryonal carcinoma	8	27
Testis	178	Seminoma	-0.5	22
Testis	178	Embryonal carcinoma	7	25
Testis	178	Teratocarcinoma	4	28
Penis	179	Queyrat's erythroplasia	3	47
Penis	179	Queyrat's erythroplasia	1	64
Penis	179	Squamous carcinoma	1	74
Kidney	180	Adenocarcinoma	3	32
Ureter	180	Transitional epithelial cancer	-4	63
Bladder	181	Transitional epithelial cancer	6	27
Urethra	181	Transitional epithelial cancer	3	22

*Includes malignancies diagnosed before condyloma (negative values) and two precancerous lesions.

TABLE III—Relative risks of cervical carcinoma in situ and genitourinary cancers in males according to length of follow up after diagnosis of condyloma

Site of cancer	1-4 years		5-9 years		≥10 years	
	No of cases	Relative risk (95% confidence interval)	No of cases	Relative risk (95% confidence interval)	No of cases	Relative risk (95% confidence interval)
Cervical carcinoma in situ	1	1.2 (0 to 6.47)	6	1.6 (0.6 to 3.4)	10	1.5 (0.7 to 2.7)
Genitourinary tumours in males	1	3.1 (0.1 to 17.4)	6	4.4 (1.6 to 9.7)	2	1.1 (0.1 to 4.1)

patients with cervical intraepithelial neoplasia are positive for human papillomavirus types 16 and 18.²⁵ The oncogenic nature of human papillomavirus is now becoming widely accepted, although direct epidemiological proof is lacking.¹⁵ Most studies to date have been retrospective—that is, the cancer is usually observed first and information about condyloma collected later. Such a study design carries a risk of many biases. It is theoretically possible that the virus entered the lesion after the cancer or cervical intraepithelial neoplasia had developed and that the transformed epithelium is tropic for human papillomavirus. Also, it is possible that some other factors—such as other venereal diseases, sperm proteins, smoking, or alcohol intake—are involved in oncogenesis in genital cancer. In a large retrospective cohort study in Rochester, Minnesota, 746 cases were identified over 29 years.^{16 17 23} The patients were routinely followed up and women were found to carry a fourfold risk of developing carcinoma in situ of the cervix. Among the 500 women, one had invasive squamous cell carcinoma, 13 had carcinoma in situ, six had severe dysplasias, and 21 had moderate to mild dysplasias in the cervix or, less often, in the vagina.¹⁷

Most authors agree that condyloma is more common in men.^{26 27} The strong male preponderance in our study might have occurred because many women with condyloma are seen at the gynaecological clinic. The male to female ratio of 3.6 to 1.0 must therefore be treated with caution, although a ratio of 7.3 to 1.0 has been reported.²⁶ The age distribution, with a peak incidence in those aged 19–24 years, is in accordance with that of most reports.^{2 16 27 28}

In this study we investigated a large number of patients with condyloma. The study population was well defined and the number of observed and expected cancers reliable owing to the accurate registration in the Swedish Cancer Registry. An increased risk of developing cervical carcinoma in situ in women with condyloma is not excluded in this study, although the results were not significant at the 95% level. In the Rochester study a significant relative risk (of 4) was observed.¹⁷ Confidence intervals were not presented, but as the data were given they can be calculated. If the variable is assumed to have a Poisson distribution and a relative risk of 4 the 95% confidence interval is 1.7 to 7.8. The results of the study therefore do not oppose our results. The age of the patients was similar in both studies. The average follow up period was longer in our

study, in which 30% of the patients were observed for 10 or more years, compared with 13% in the Rochester study. Our method of calculating the expected number of patients with cervical carcinoma in situ is more accurate. Interestingly, the same ratio of women developed cervical carcinoma in situ after condyloma was diagnosed in both studies (17 out of 711 (2.4%) in our study compared with 13 out of 500 (2.6%) in the Rochester study). The Rochester authors estimated the incidence of cervical carcinoma in situ in their population by applying the incidence in 1960–7 to the follow up in person years for patients with condyloma diagnosed during 1950–78. We calculated the expected number of cancers individually for each patient by using age and calendar specific incidence data for the corresponding years. The incidence of cervical carcinoma in situ tends to vary yearly (fig 2), and a steady increase occurred from 1968.¹⁹ The steep rise from 1964 to 1968 was probably due to undernotification during the first years after registration of cervical carcinoma in situ became compulsory, better diagnostic awareness, and true increase in incidence. Although this early rise might have been partly due to undernotification, it is important to use these data when predicting the incidence of cervical carcinoma in situ during that period because it is likely that reporting of the disease to the registry would have been influenced by the same factors. Obviously the quality of the incidence data is of crucial importance and strongly affects the relative risks. Our results indicate that the risk of developing cervical carcinoma in situ might be less than previously thought. The follow up may have been too short, but this is not likely as no increased risk was observed in patients followed up for more than 10 years after diagnosis.

No increase in the number of patients with invasive cervical carcinoma was observed. The observation period may have been too short, the data insufficient, or the risk less than previously thought. Also, because of screening, many cancers are diagnosed at the in situ stage and therefore never reach the invasive stage. Our results do not exclude the hypothesis that genital human papillomavirus infection is a risk factor for development of cervical cancer. It is even possible that because they have condyloma the patients are under closer observation, which leads to early detection of cancer at the in situ stage and hence a lower incidence of invasive cancer.

Male patients with condyloma had an increased risk of developing cancer (at all sites). Most of this increased risk was for genitourinary tumours, which were significantly increased. There was no significant increase in risk for tumours at individual genitourinary sites, but if the single testis cancer which was diagnosed six months before the condyloma was included there was a relative risk of 3.5 (1.1 to 8.4) for developing a testicular malignancy. This approach can be questioned, as traditionally only cancer that is diagnosed

FIG 2—Changes in incidence of cervical carcinoma in situ in women aged 25–29 (based on figures from Swedish Cancer Registry)

after diagnosis of condyloma would be considered. In this case, however, it is not a question of whether condyloma causes cancer, but rather that both the condyloma and the malignancy are caused by human papillomavirus. It is therefore possible that the patient had had the human papillomavirus infection for some time before the condyloma developed. Also, the nature of condylomatous disease is such that it does not require immediate medical attention.

A possible explanation for this increased risk is that the virus might, in a similar way as predicted in women, infect the epithelium and predispose to cancer. Oncogenic human papillomavirus types have been found in prostatic tissue, but the potential role of human papillomavirus in the aetiology of urogenital neoplasia remains to be shown.²⁹ Also, it must be emphasised that with multiple statistical testing significant results may be obtained in one or more of the tests without there being any biological significance. We do not think this likely in this study, as the incidence of cancer was increased on the whole and most of this risk was for genitourinary tumours, but further studies are needed to elucidate the association between anogenital human papillomavirus infection and genitourinary cancer in men.

The current study design avoids many of the possible biases that might lead to a false conclusion.³⁰ The most important bias is the Berkson bias,³¹ in which the joint occurrence of two diseases becomes more likely with selective referral of patients with both conditions. This is unlikely to have had any effect on our results as development of cancer was studied after the development of condyloma. A second bias, the withdrawal bias, occurs when the subjects who remain in the study have a higher frequency of the associated disease. Our study design eliminates this bias. The third bias, diagnostic suspicion, occurs when patients included in the study are evaluated more thoroughly for the putative associated disease. As the association between condyloma and cervical cancer has been suspected for a long time, it cannot be excluded that cervical carcinoma in situ is diagnosed earlier in this patient group. The effects of this bias are minimised, however, by the use of the cancer registry.

It might be argued that the fact that some patients are seen at the gynaecological department leads to a selection among female patients, with relatively fewer patients with condyloma on the portio in this study. We do not believe this bias to be important because many "mild" cases of condyloma are diagnosed in the gynaecology department when the patients attend for something else (abortion, preventive counselling, etc). Also many patients have lesions on the portio diagnosed in the dermatology department, although they are finally treated at the gynaecology department. Walker *et al* have shown that 50% of women with "external" condyloma also have cervical involvement.³²

Finally, more studies are needed to answer fully the question, does human papillomavirus infection cause cancer? Most studies have suggested that human papillomavirus types 6 and 11 are associated with

condyloma while types 16 and 18 are associated with cervical neoplasia. It is therefore important to investigate further the development of cancer in patients with known types of human papillomavirus.

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