

Ladies and Gentlemen,

The question as to the »sequence of anal condylomata acuminata with and without dysplasia and transition in carcinoma in situ and invasive carcinomas of the anal canal« is not new. It was already investigated more than 10 years ago with the means available at that time. In situ DNA hybridization resp. the DISH technique or, less often, PCR with various primers for human papillomaviruses were mostly used. Human papillomaviruses were found with various incidences both in condylomas and in carcinomas of the anal canal. In most cases, HPV type 16 and –later- HPV type 18 were the target of investigations. In recent years, a low-risk HPV and a high-risk HPV group have emerged within human papillomaviruses. As the name already indicates, a different significance for various biological characteristics are clearly attributed to these.

In methodological terms, we have proceeded by cutting and slicing paraffine embedded formol fixed samples or by removing the corresponding epithelial parts of the condylomatous lesions from the microscope slide resp. by scratching them off and processed them for further molecular pathological investigation. In the presence of HPV DNA in general, the presence of the L1 locus in the genome was looked for by means of consensus PCR. When the result was positive, high and low-risk HPV were identified with the hybrid capture method I. Fig. 1 demonstrates these two groups, comprising the different HPV types.

The following results were obtained:

To get an overview over the normal distribution of age and sex we analyzed all samples out of the anal region in this respect from 1993 – 1999 (Sept.).

As can be seen in this slide, all investigations of the anatomical region of the anal canal show an age peak in the third to fifth decade of life to the same extent in men and women and an even decrease in both sexes. However, there is preponderance of the female sex with increasing age. Fig.2.

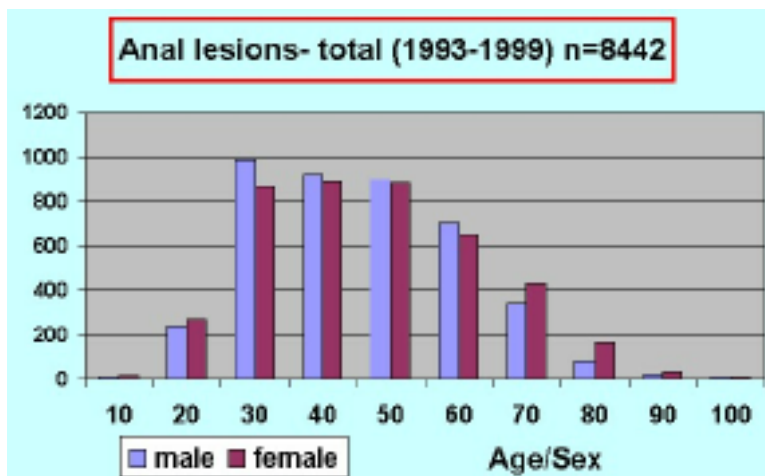


Fig.2 : Distribution of age und sex of all samples out of the anal region within a large cohort

In the group of anal condylomata acuminata without dysplasias, more or less there is an equal distribution of both sexes. The detection of HPV DNA does not reveal any appreciable differences. Out of a total of 519 anal condylomas without dysplasias, HPV DNA could not be detected in about half of the cases, i.e. 251 cases or 48.4%. Accordingly, HPV DNA was detected in more than half of the cases (i.e. 51.6%). With regard to the differentiation between low-risk HPV, high-risk HPV and »HPV DNA of currently unknown significance«, there were no significant differences between men and women. The latter group comprises those cases with positive results in the consensus PCR for L1 (MYC 9 and MYC11) but lacking further viral detection, that is negative in the liquid phase (hybrid capture). Fig.3.

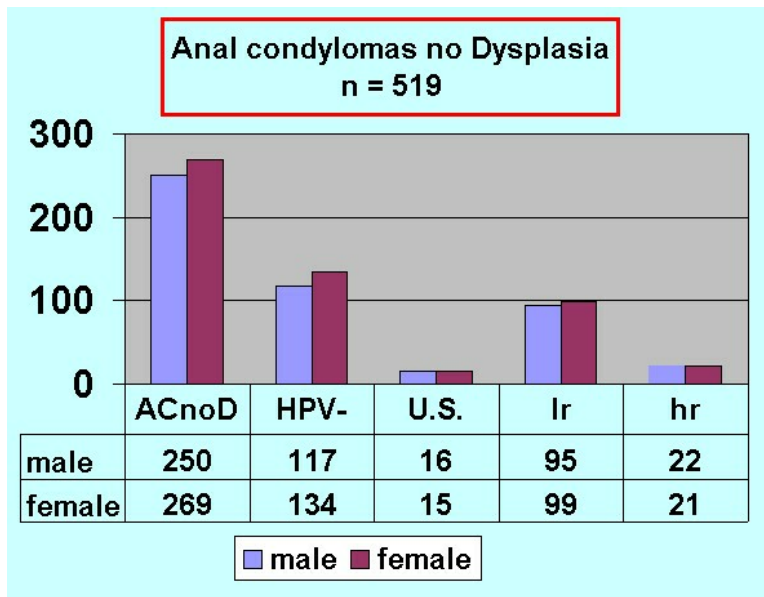


Fig. 3: Anal condylomas without dysplasia

Within the group of 625 **anal condylomata acuminata with dysplasias**, no HPV DNA could be detected in 103 cases (16.5%). Accordingly, 522 cases (83.%) revealed HPV DNA. 272 women (52.2%) and 250 men (47.8%) were affected, i.e. there is an almost equal involvement of both sexes with a slight preponderance of women. However, if a distinction is made according to the individual HPV types, there is significant involvement of women both by »HPV of unknown significance« as well as high-risk HPV is shown. Low-risk types HPV predominate, i.e. 139/63 or 68.8% involved male patients as compared to about one third (31.2%) of female patients. However, in the high-risk group, females were affected very much more frequently: of a total of 71 cases, 42 (59.2% or almost 60%) were women and the remainder, i.e. only 40.8%, were men. Fig.3.

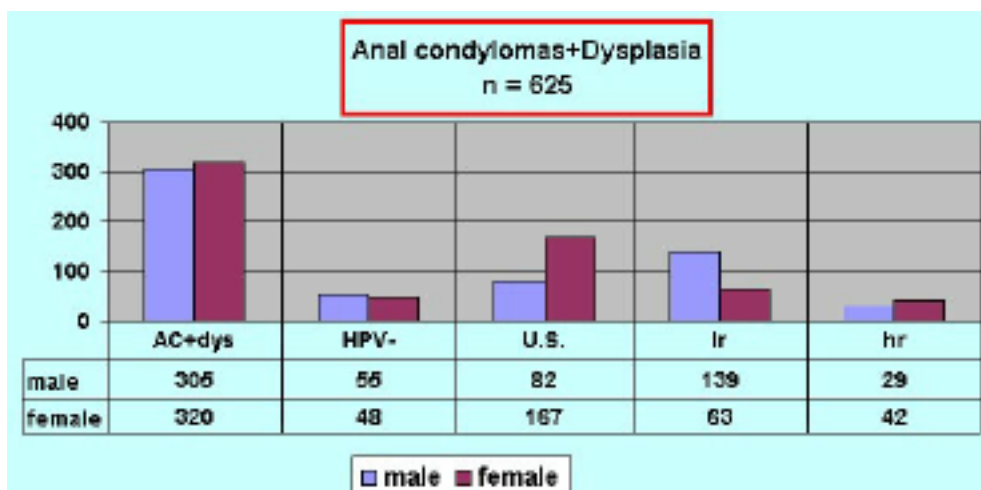


Fig.4 : Anal condylomas with dysplasia

The situation is even more striking in respect of anal carcinomas: women are more frequently affected in almost two thirds of cases: 25/39 cases or 64.1% than men (14/39 or 35.9%). Moreover, high-risk group HPV significantly predominated with an incidence of 67.4%.Fig.5.

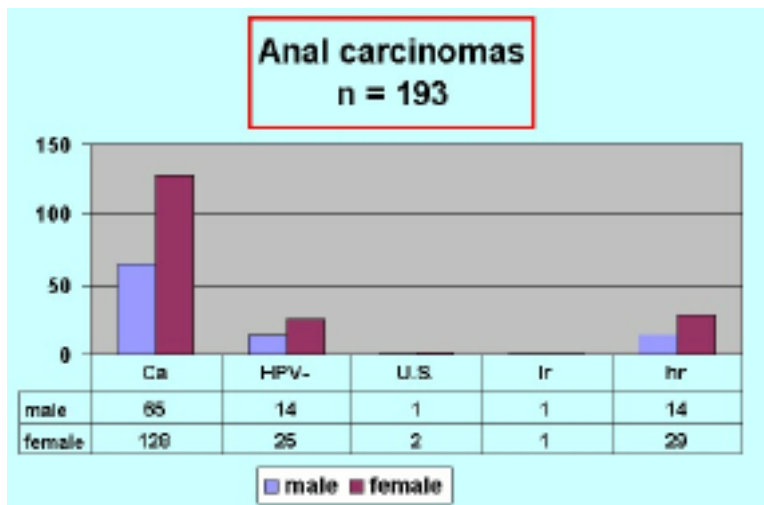


Fig. : Anal carcinomas. From a total of 193 carcinomas 87 cases were investigated for different HPV types

From a purely morphological point of view, there is neither an explanation for the above-average high occurrence of anal carcinomas in women nor for the exceedingly high incidence of high-risk HPV. Infection with high-risk HPV doubtless has great importance with regard to the etiology and pathogenesis of anal carcinoma in women. However, the infection with HPV of the high-risk group does not explain on its own the significantly higher occurrence of anal carcinomas in women.

In recent years, changes in the cellular immune defense, especially a local weakness in resistance as a result of lack of macrophages, immunocompetent CD8-positive lymphocytes and CD45R0-positive T lymphocytes as well as life style (e.g. smoking) have been discussed. These hypotheses have not been validated at present since appropriate large-scale investigations have not yet been carried out.

From a morphological point of view, further predisposing factors which favor the development of anal carcinoma in women must be postulated.

For this reason, I should like to conclude my paper with the following provocative questions:

1. Why do anal carcinomas occur more frequently in women than in men?
2. Why is high-risk HPV demonstrated with an above-average higher frequency in anal carcinomas of women than in men?

The present investigations should stimulate a quest for such factors in the future.

Thank you for your attention.