Cervical cancer

2022-RA-136-ESGO COLUMNAR EPITHELIUM IS THE ORIGINAL SITE OF MOST CERVICAL SQUAMOUS CELL CANCERS

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Introduction/Background Cervical HPV-research is based on mature squamous epithelium (Woodman, CB. Nat Rev Cancer 2007), however, only a minority of squamous cell cancer (SCC) arise in this type of epithelium. Surprisingly, it was only in the last years that immature squamous metaplastic epithelium in the transformation zone and reserve cells (RC) throughout the columnar epithelium moved into research focus.
Methodology This review will focus on recent aspects of HPV-induced cervical carcinogenesis.
Results UGS-derived p63/CK17-positive RC located within the columnar epithelium are precursor cells for metaplastic squamous epithelium and subsequent HSIL and SCC (Fritsch, Clin Ant 2021; Regauer S. Curr Opin Virol 2021). RC may be target for HPV-infection and act as reservoirs of HPV (Goyal A, Am J Surg Path 2020; Doorbar J, Curr Opin Virol 2021). A HPV-infection of proliferating RC and immature metaplasia that is not controlled by the immune system, allows development of small foci of thin HSIL as result of inhibition of p53- and Rb-protein-mediated cell-cycle processes by E6/7-protein (Reich, Int J Gynecol Pathol 2017; Regauer, Am J Surg Pathol 2021; Regauer, Curr Opin Virol 2021). Enlargement of thin HSIL and stepwise progression from thin to thick HSIL eventually produce larger lesions, and invasion begins from thick HSIL inside the TZ.
Conclusion Contrary to the prevailing opinion, cervical SCC arise most frequently from RC and immature metaplastic epithelium in the TZ. Cervical carcinogenesis is not limited to the SCJ, and cuboidal cells, that accomodates for the difference of epithelial thickness at the SCJ, are of no significance for carcinogenesis.

2022-RA-137-ESGO DIFFERENTIATED CERVICAL INTRAEPITHELIAL NEOPLASIA (D-CIN) REPRESENTS A RARE HPV-INDEPENDENT PRECURSOR LESION OF SQUAMOUS CELL CANCER

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Introduction/Background Although our knowledge of HPV-independent squamous cell cancers (SCC) of the cervix is growing, the current 2020 WHO classification does not describe HPV independent cervical precancers. The main reason for this was that these exceedingly rare cervix HPV-independent precancerous lesions were not described at time of publication.
Methodology This review will focus on recent aspects of HPV-independent cervical carcinogenesis.
Results In 2020 we reported for the first time a preinvasive cervical lesion negative with 3 different HPV tests in a series of 474 cone specimens (Reich O. Gynecol Oncol 2020). In 2022 we demonstrated detailed characteristics of HPV-negative cervical intraepithelial precursors (Regauer S. Am J Surg Path 2022). HPV-negativity was defined as lack of both, DNA of 32 HPV subtypes and E6/E7 mRNA of 14 HPV subtypes, and additionally by the absence of HPV sequences in ~5 Mio´s WGS reads. The morphological hallmark of this cervical lesion was the presence of atypical keratinocytes confined to the basal and parabasal layers in squamous epithelium with hyper- and parakeratosis with elongated rete ridges. The subepithelial stroma had a dense inflammation with plasma cells and eosinophilic granulocytes. Finding an appropriate terminology for these differentiated intraepithelial precursor lesions, however, proves difficult. In analogy to terminology of vulvar carcinogenesis, differentiated cervical intraepithelial neoplasia (d-CIN) may be appropriate.
Conclusion The existence of primarily HPV-negative squamous cervical precancers (d-CIN type and basaloid type) needs to be recognized (Regauer S. Int J Gynecol Cancer 2022). In a future classification squamous intraepithelial cervical precancers should be grouped into two categories: HPV-associated and HPV-independent.

2022-RA-141-ESGO GENOMIC CHARACTERISTIC ANALYSIS IN SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA OF CERVIX IDENTIFIES ALPELISIB AS A THERAPEUTIC OPTION FOR PIK3CA MUTATIONAL CERVICAL CARCINOMA

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Introduction/Background Cervical squamous cell carcinoma (CSCC) and cervical adenocarcinoma (CAdC) are the two most histological types in cervical carcinoma, with unequal outcomes and unclear mechanisms in tumor biology. We aim to explore the genomic characteristics between them and identify a promising target for cervical carcinoma.
Methodology We analyzed the genomic data of cervical carcinoma to identify genomic characteristics between SCC and CAdC. *In vitro* and *in vivo* assays were performed to testify the therapeutic effects of Alpelisib in PIK3CA mutational cervical carcinoma. Mutation analysis, Enrichment and pathway analysis, and co-immunoprecipitation were used to demonstrate the mechanisms of Alpelisib in cervical carcinoma.
Results CSCC showed higher point mutation density, high copy number cluster, low to intermediate CpG island methylator phenotype (CIMP) compared with CAdC, with the enrichment in the RTK/PI3K/MAPK pathway. In addition, point mutation of PIK3CA (P=0.0401) was significantly observed in CSCC, with different overall survival (P=0.0469) between the two histological types. *In vitro*, PIK3CA mutational cell lines (ME-180 and Ca-Ski) showed higher sensitivity to Alpelisib than cell lines without PIK3CA mutation. The correlation genes of PIK3CA in cervical cancer showed the enrichment of