Reviewer's code: 00862649

1. The levels of the immune cell subsets as they related to histological phenotype and HPV were not dramatically correlated, but it was a worth while analysis.

Kim et al. revealed that the decreased number of CD8+ T cells was significantly associated with aggressiveness and malignant features of tumors, including lymph node metastasis, higher stage and high Ki67[13].

Reviewer's code: 03478911

1. The theoretical description of HPV types was lack.

HPV types are classified as low-risk and high-risk types based on the hability to induce carcinogénesis. HPV 6 and HPV 11 are low-risk subtypes and cause more tan 90% of genital warts. High-risk HPV subtypes such as HPV 16,18, 31, 33, 45 and 52, cause squamous intraepithelial lesions that can progress to invasive squamous cell carcinomas[10].

2. Molecular subtypes classification of immune cells.

For each group, the cellular subsets counts average were calculated.

3. System of immunity might change following age.

It is known that functional capacity of immune cells decline with ageing. A diminished phagocytic capacity of dendritic cells leads to impaired antigen presentation and activation of the adaptive immune system. Besides, thymus involution decreases the production of naïve T cells, and memory T cells accumulate diminishing the T-cell repertoire[44,45].

Postmenopausal women exhibit a reduced number of total lymphocytes, mainly B and CD4+ cells. Similarly, after surgical menopause, the CD4+/CD8+ ratio and the circulating B cells are decreased, while NK cells are increased[45]. The breast cancer patients evaluated did not show statistically significant differences with respect to cell subsets and age groups (data not shown).

4. Association of HPV infection with the ration of the CD8+ cells (Discussion).

It is known that CD8+ T cells play a major role in elimination of viral infection, secreting IFN and displaying cytolytic effects mediated by granzyme and perforin. CD4+ T cells also secrete IFN and instead mediate killing primarily by engagement with ligands for death receptors such as Fas or TRAIL, resulting in caspase-mediated apoptosis[49].

Reviewer's code: 02510728

1. The importance of the CD3, CD4 and CD8 should be emphasized in cancer recurrence and overall survival.

Besides clinical and treatment parameters, the host immune response might influence the prognosis of cancer patients after standard treatment[13].

CD8+ T cells have been shown to be mediators of antitumor immunity and act directly over tumor cells. Recent studies has been suggested its clinical importance, reporting that an increase of CD8+ T cells correlates with increased survival in large cohorts of various human cancer patients[13].

NK cells appears to protect against tumor development and progression[17].

2. The Number of patients is low. It is difficult to decide statistically.

Is the first study reported in Venezuela, also the sanitary conditions in our country make more difficult increase the number of patients.

3. The Non genetic factors (age, menarche etc) in the introduction is repeated in the discussion. This parragraph must be removed from introduction section.

It was removed in the discussion.

4. The mechanism of HPV-induced tumors is different and emphasizes the differentiation from the mechanism of breast cancer

Recently, several studies focused on DNA Deaminase APOBEC3B (A3B), as a source of uracil dependent genomic mutations and associated with mutagenesis in multiple human cancers, including breast cancer, head and neck, cervix, bladder, lung, ovaries and other tissues. This enzyme belongs to a protein family that has broad and overlapping functions in innate immunity by restricting viruses, transposons and other foreign DNA elements[38]. Therefore, some authors suggest a possible rol for viral infections, such as HPV and EBV, on the regulation of the expression of the A3B gene, in some cases of breast cancer[38,39].

Due to the low expression levels in most of normal tissues, a mechanism that could be affecting this A3B protein arises. The E6 HPV oncoprotein offers the first contact in viral

infection and A3B-mediated mutagenesis. A model in which high-risk HPV E6 protein inactivate p53, causing the elimination of A3B gene transcription was proposed[38], for cervix cancer, head and neck[40], and now, HPV positive breast cáncer[39], where the proteins p53, A3B and E6 are involved, raising the levels of DNA damage and mutations, and preventing answers to these damages and apoptosis.