Abnormal Oral Phenotypes as a Risk Factor for Cancer: Hypodontia and Ovarian Cancer

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There are over 300 genes involved in odontogenesis, and alteration of any can result in hypodontia. Many of these genes have also been found to play a role in other bodily systems. This study looks specifically into hypodontia (excluding missing third molars), missing permanent teeth specifically due to agenesis, as a possible risk marker for epithelial ovarian cancer (EOC) in women. Ovarian cancer is the most fatal malignancy of the female genital tract, and has no known early diagnostic markers or effective treatments. Ovarian cancer is most often diagnosed in women 55 years of age or older and when this age group is examined, 1 in 67 women are diagnosed with EOC. Most common genes associated with EOC are currently BRCA1 and BRCA2 tumor suppressor genes.

With recent advances in genetic testing and research seemingly unrelated conditions have had identified associations that were previously unknown. Some of the following associations between the abnormal oral phenotype of hypodontia and cancer found elsewhere in the body have already been identified:

- Association between hypodontia and colon cancer via a mutation in Axis Inhibition Protein 2 (AXIN2). This gene is involved in embryonic development and cellular homeostasis via the Wnt signalling pathway. This pathway is involved in proliferation, differentiation and morphogenesis of most organs
- Association between hypodontia and increasing malignancy of dysplastic and carcinomas of the esophageal epithelium via a loss or reduction of Paired Box 9 (PAX9) gene expression. This gene regulates spatial and temporal regulation of odontogenesis during the initiation and bud stage of development

Prevalence of hypodontia ranges from 2.6 to 11.3 percent, females more affected than males. Most commonly the mandibular second premolars are affected, followed by the maxillary lateral incisors. Hypodontia can have single gene familial inheritance. It has been identified that autosomal dominant inheritance of genetic mutations are the most common forms of transmission. Hypodontia can also have multifactorial inheritance of which we currently cannot identify the genetic influences at play.

It was hypothesized by this study that due to the early presentation of hypodontia, if the prevalence rates of hypodontia among females with EOC were significantly different than those without EOC, then a genetic association may be present. This would create a potential risk marker for EOC that would greatly lower the detection age for those at risk of developing EOC.

100 Women with EOC served as the population for this study and their dental histories were collected:

- The prevalence of hypodontia (1-2 missing teeth) was 20% in women with EOC
- The prevalence of hypodontia was 3% in the control group of women without EOC
- 30% of women with EOC and hypodontia reported a family history of ovarian cancer

    - Zero women in the control group (no EOC) with hypodontia had a family history of ovarian cancer

- The odds ratio developed from this study concluded that women with EOC are 8.1 times more likely to have hypodontia than women without EOC

This study went further to name specific genes involved in epithelial cell growth and odontogenesis, that when mutations are present, have shown to show phenotypes of ovarian cancer and hypodontia.

- MSX1: Msh Homeobox 1 is a gene involved in the regulation of p53 tumor suppressor genes.
- AXIN2: Axis Inhibition Protein 2 is a tumor suppressor gene

Two genes this study identifies as requiring further molecular and genetic testing to identify if there is involvement in both odontogenesis and ovarian cancer development are the following:

- BARX1/BARX2: BARX Homeobox 1/2 is a transcriptional regulator of cell adhesion molecules and possible tumor suppressor gene. Specifically, this is expressed during craniofacial development however hasn't been implication in hypodontia.
- PAX9: Paired Box 9 maintains cellular differentiation in keratinocytes of the esophagus, has been identified with hypodontia but has not been studied in ovarian cancer.

This study identified a possible relationship between hypodontia and EOC. A mutation in genes involved with embryonic development (including tooth development), causes hypodontia which can be identified early in life via missing permanent teeth in the first two decades of life. These mutations in the same genes may result in the development of cancer later in life, specifically creating hypodontia a potential risk marker of future ovarian cancer development.

Take Home Message

Ovarian cancer is the most fatal malignancy of the female genital tract, and has no known early diagnostic markers, often diagnosed in women over 55 years of age and without effective treatments. The same genetic mutations in genes involved in embryonic development that cause hypodontia, one or two missing permanent adult teeth, are possibly involved with the development of epithelial ovarian cancer. In one case-control study, it concluded that women with epithelial ovarian cancer are 8.1 times more likely to have hypodontia than women without epithelial ovarian cancer. This study suggests hypodontia, which can be seen early in one's life, as possible risk marker of future epithelial ovarian cancer development. The association is stronger when familial history of EOC is present.

References

Hypodontia as a risk marker for epithelial ovarian cancer. Chalothorn, Leigh A. et al. The Journal of the American Dental Association , Volume 139 , Issue 2 , 163 - 169