

# Hypodontia and ovarian cancer: A systematic review

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## Abstract

Hypodontia can be defined as the non-formation of one or more teeth during the developmental period. Mutation in several genes related to tooth formation has previously been correlated with cancer. Regarding the ovarian cancer, there are few studies that associate the presence of hypodontia with ovarian cancer. A systematic literature search was performed in PubMed and Scopus. In total, 385 patients were included in this study. Control group was present in 3 out of 4 studies (340 patients). Hypodontia was present in 56 out of 290 patients (incidence of 19.3%). Only in 2 out of 4 studies, the number of missing teeth was mentioned (47 teeth), while the majority of them were either maxillary second premolars or maxillary lateral incisors. Unilateral distribution of the missing teeth was present in 28 out of 46 patients, while bilateral distribution of the missing teeth was present in 18 out of 46 patients. The presence of ovarian cancer in the family medical history occurred in 12 out of 33 patients. Only 1 out of 4 studies examined the presence of genes with mutations in the included patients. Based on our findings, the lack of clinical studies was the principal obstacle to clarify the possible predictive value of hypodontia in the early prediction of patients with higher risk of ovarian cancer. (J Turk Ger Gynecol Assoc 2016; 17: 41-4)

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## Introduction

Hypodontia or selective tooth agenesis can be defined the non-formation of one or more teeth (<6 teeth) during the developmental period combined with variations in size, shape, and eruption time (1). The worldwide prevalence ranges between 2.6% and 11.3% (2, 3). Women are affected more than males at a ratio of 3:2. Hypodontia may be presented either as part of a clinical syndrome or as a non-syndromic form, the latter being more frequent. Both genetic and environmental explanations for hypodontia have been reported (1). More than 300 genes are involved in odontogenesis (4). Mutation in several genes related to tooth formation has previously been correlated with cancer (5-7). Regarding the ovarian cancer, there are few studies that link the presence of hypodontia with ovarian cancer. The purpose of our study is to review the available literature on the correlation of hypodontia and ovarian cancer.

## Methods

### Data sources

A systematic search was performed in PubMed (May 1, 2015) and Scopus (May 1, 2015) to retrieve the included studies. The applied search strategy, in all the searched databases, included the combination of the key words: hypodontia and ovarian cancer. For additional studies, the references of the included articles have also been hand-searched.

### Study selection criteria

All the studies that reported data on the presence of hypodontia and ovarian cancer were included in this review. Abstracts in scientific conferences, animal studies, editorials, letters to the editor, review articles, and studies published in languages other than English, German, Greek, French, Italian, and Spanish were excluded from this review. The retrieved data from each of the included studies were focused on the publication type, the number of patients included in each study, the number of patients included in the control group, the incidence of hypodontia, the number of missing teeth, the type of missing teeth, the distribution of hypodontia, the presence of ovarian cancer in family medical history, and the presence of isolated genes correlated to ovarian cancer.

## Results

The performed search in PubMed and Scopus revealed a total of 43 and 39 search results, respectively, among which 4 studies (4 case series) were identified as eligible for inclusion in this review, according to the inclusion criteria (8-11). No additional studies were identified by searching the references of the included studies. The selected studies for inclusion are presented in detail in Figure 1 (flow diagram).

The principal characteristics of the included studies in our review (publication type, number of patients, control group, incidence of hypodontia, number of missing teeth, type of miss-



**Table 1. Studies reporting data regarding the correlation of hypodontia with ovarian cancer**

First author, year, country (Ref)	Publication type	No. of patients	Control group	Incidence of hypodontia (%)	No. of missing teeth	Type of missing teeth (%)	Distribution of hypodontia (%)	Presence of ovarian cancer in family medical history (%)	Isolated genes (%)
Fekonja et al. (8), 2015, Slovenia	retrospective study	120	120	23/120 (19.2)	NM	NM	Unilateral: 10/23 (43.5) Bilateral: 13/23 (56.5)	9/23 (39)	NM
Bonds et al. (9)*, 2014, USA	retrospective study	95	-	NM	NM	NM	NM	NM	BRCA1: 7/50 (14) EDA: 1/50 (2) WNT10A: 6/50 (12) AXIN2: 1/50 (2)
Fekonja et al. (10), 2014, Slovenia	NRCT	120	120	23/120 (19.2)	31	maxillary SP: 14/31 (45.1) maxillary LI: 10/31 (32.3) mandibular SP: 5/31 (16.1) mandibular CI: 2/31 (6.5)	Unilateral: 18/23 (78.3) Bilateral: 5/23 (21.7)	NM	NM
Chalothorn et al. (11), 2008, USA	NRCT	50	100	10/50 (20)	16	maxillary LI, maxillary SP	NM	3/10 (30)	NM

USA: United States of America; y.o.: years old; NM: not mentioned; NRCT: non-randomized controlled trial; SP: second premolars; LI: lateral incisors; CI: central incisors; BRCA1: breast cancer 1; EDA: ectodysplasin A; WNT10A: wingless-type MMTV integration site family member 10A; AXIN2: axis inhibition protein 2  
\*Refers to patients included in the Chalothorn et al. (11) study

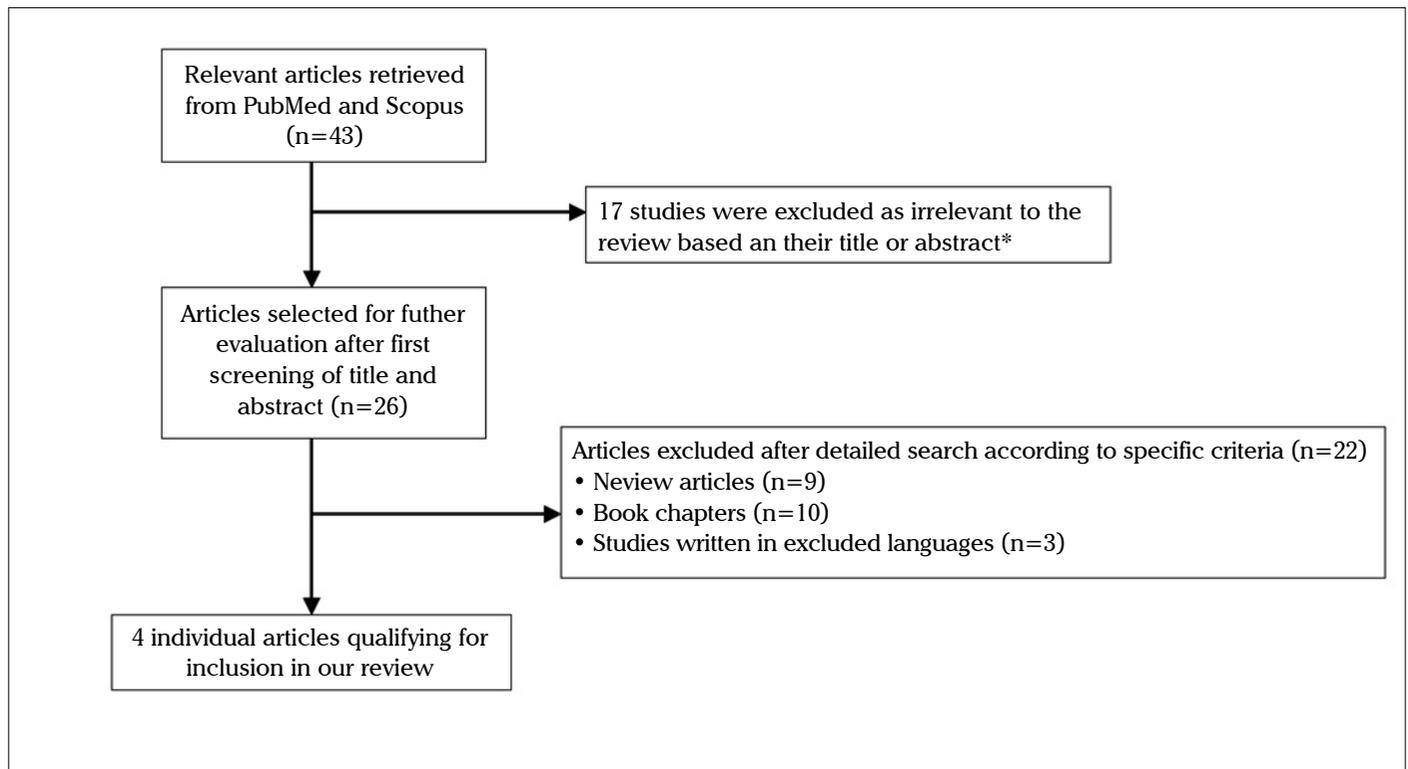
ing teeth, distribution of hypodontia, presence of ovarian cancer in family medical history, and isolated genes) are presented in Table 1. In total, 385 patients were included in this study. Control group was present in 3 out of 4 studies (340 patients). Hypodontia was present in 56 out of 290 patients (19.3%). Only in 2 out of 4 studies, the number of missing teeth was mentioned (47 teeth), and the majority of them were either maxillary second premolars or maxillary lateral incisors. Unilateral distribution of the missing teeth was present in 28 out of 46 patients, while bilateral distribution of the missing teeth was present in 18 out of 46 patients. The presence of ovarian cancer in the family medical history occurred in 12 out of 33 patients. Only 1 out of 4 studies examined the presence of genes with mutations in the included patients. Specifically, breast cancer 1 (BRCA1) gene and wingless-type MMTV integration site family member 10A (WNT10A) gene was present in 7 and in 6 out of 50 patients, respectively.

## Discussion

Tooth embryogenesis is controlled by migration of neural crest cells that specialize in formulating specific type teeth. Genetic

control during embryogenesis could be related to teeth shape, type, affiliation, and prolapse with the help of homeobox genes such as msh homeobox (MSX) 1 and MSX2 (12). Hypodontia is the most common congenital anomaly of the teeth (13). The data so far suggested that the prevalence is around 3.5-6.5% of the general population; however, it is higher in Africa, where it reaches 13.4% (1). Our review of the current studies revealed an incidence of 19.3% in patients with ovarian cancer.

It is thought to be a multifactorial condition related both to genes as well as environmental effect. In recent studies, it was shown that genes related to hypodontia could also be related to ovarian cancer as women with hypodontia have 8 times higher risk of ovarian cancer (11). Some of the genes that are related to hypodontia are paired box 9 (PAX9), MSX1, and axis inhibition protein 2 (AXIN2) (14, 15). WNT10A is the most commonly mutated gene in hypodontia (16). These genes are also expressed in tumor cells of the female reproductive system. Hypodontia was also associated with positive self-reported family history of cancer and with variants in genes fibroblast growth factor 3 (FGF3), FGF10, and FGFR2 (17). However, BRCA genes show no evidence of involvement in



**Figure 1. Flow diagram of the selection process of the included articles in the review**

\*The majority of studies were found in both databases

hypodontia, although they are highly associated with ovarian cancer (9). Regarding environmental effect, it is related to early radiation of dental germ, thalidomide, osteomyelitis, or moving the dental germ of the permanent tooth during extraction of milk teeth (18). A family history could be related to hypodontia; however, there is no correlation with maternal health problems during pregnancy (13). Hypodontia is also related to extradermal dysplasia, cleft lip and palate, van der Woude syndrome, and Down syndrome (18).

The teeth that are mainly related to hypodontia are maxillary second premolars or maxillary lateral incisors (10). The lower premolars are usually missing in the Caucasians, while the lower lateral incisors in the Chinese population (10). Our review confirmed that the majority of the teeth are either maxillary second premolars or maxillary lateral incisors. Unilateral distribution of the missing teeth was present in 60.8% of the patients included in the review.

Different parameters are correlated with ovarian cancer such as history of diabetes mellitus or endometriosis (19, 20). The review of the current literature reveals strong correlation between hypodontia and ovarian cancer. Recently, Fekonja et al. (8) performed a subanalysis of their data showing that bilateral ovarian cancers are more common than unilateral in patients with hypodontia, and these patients have a higher incidence of other malignant tumors as well compared to controls. However, Lindor et al. (21) did not find any correlation of colorectal cancer with hypodontia. On the other hand, it was also revealed that there is no correlation of hypodontia with histological ovarian cancer subtype, but a statistically significant

difference was found in regard to stage and grade compared to the control group (8).

Our review supports a possible correlation between hypodontia and ovarian cancer, and for this reason, hypodontia could potentially become a risk marker for future ovarian cancer development. A future step could be the earlier referral of such patients for ovarian cancer screening. According to van Nagell et al. (22), if a correlation was found between hypodontia and ovarian cancer in more prospective studies, then semiannual screening should become the standard of care for those women in order to achieve earlier detection.

Before reaching any conclusion, there are several limitations that should be taken into consideration. The limited number of the existing studies and, as a consequence, the small number of the included patients cannot allow us to draw any safe conclusion. However, our review reveals quite a strong correlation between hypodontia and ovarian cancer. Regarding the adopted search strategy, this could be considered as restricted due to the exclusion of abstracts in scientific conferences, review articles, conference papers, letters to the editor, animal studies, and editorials, while the limitation based on the language of the excluded articles could also be considered another weakness of this study.

## Conclusion

Based on our findings, we believe that more prospective or retrospective studies should be organized in order to clarify the possible predictive value of hypodontia in the early prediction of patients with higher risk of ovarian cancer.

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