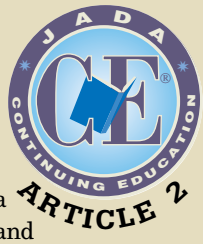
Hypodontia as a risk marker for epithelial ovarian cancer

A case–controlled study

Leigh A. Chalothorn, DMD, MS; Cynthia S. Beeman, DDS, PhD; Jeffrey L. Ebersole, PhD; G. Thomas Kluemper, DMD, MS; E. Preston Hicks, DDS, MS, MSD; Richard J. Kryscio, PhD; Christopher P. DeSimone, MD; Susan C. Modesitt, MD

Recent advances in genetic research have allowed for a greater understanding of the underlying causes of human disease, furthering the exploration and insight into possible genetic associations among seemingly unrelated conditions. More than 300 genes are involved in odontogenesis, and mutations in several of these genes have been linked with hypodontia.[1,2] The genes that control the development of teeth also have important functions in other organs and body systems. Therefore, it is plausible to assume that a genetic mutation resulting in hypodontia also may cause abnormalities in other parts of the body. A 2004 study by Lammi and colleagues[3] revealed a possible molecular association between hypodontia and colon cancer via a mutation in the axis inhibition protein 2 (*AXIN2)* gene, which is involved in embryonic development and overall cellular homeostasis via the regulation of many biological signaling pathways, specifically the wingless type (Wnt) signaling pathway.[3-5] Researchers also have shown that a loss or reduction of

ABSTRACT



Background. Genetic mutations that result in hypodontia also may be associated with abnormalities in other parts of the body. The authors conducted a study to establish the prevalence rates of hypodontia among subjects with epithelial ovarian cancer (EOC) and control subjects to explore possible genetic associations between these two phenotypes.

Methods. The authors recruited 50 subjects with EOC and 100 control subjects who did not have EOC. The authors performed a dental examination on each subject to detect hypodontia, and they reviewed pertinent radiographs and dental histories. They also recorded any family history of cancer and hypodontia.

Results. The prevalence of hypodontia was 20 percent for EOC subjects and 3 percent for control subjects. The difference between these two hypodontia rates was significant. This difference implied that women with EOC are 8.1 times more likely to have hypodontia than are women without EOC. The severity of hypodontia was similar between the two groups, with one to two teeth being affected. Maxillary lateral incisors followed by second premolars were the most frequently affected teeth.

Conclusion. The preliminary data suggest a statistical association between hypodontia of the permanent dentition and EOC.

Clinical Implications. Genetic analysis of the genes of interest is necessary to explore similarities between hypodontia and EOC further. An association could allow hypodontia to serve as a potential risk marker for EOC.

Key Words. Ovarian cancer; DNA; hypodontia; genetics; tooth.
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Dr. Chalothorn was a student, Division of Orthodontics, University of Kentucky, Lexington, when this study was conducted. She now is in private practice in orthodontics, Lexington, Ky. Address reprint requests to Dr. Chalothorn at 1009 Firethorn Place, Lexington, Ky. 40515, e-mail "leighchalothorn@yahoo.com".
Dr. Beeman is an associate professor and the research director, Division of Orthodontics, University of Kentucky, Lexington.
Dr. Ebersole is the associate dean for research and graduate studies and the director, Center for Oral Health Research, University of Kentucky, Lexington.
Dr. Kluemper is an associate professor and the chief, Division of Orthodontics, University of Kentucky, Lexington.
Dr. Hicks is the program director and an associate professor, Division of Orthodontics, University of Kentucky, Lexington.
Dr. Kryscio is a professor, Department of Biostatistics, University of Kentucky, College of Public Health, Lexington.
Dr. DeSimone is an assistant professor, Gynecologic Oncology, University of Kentucky, Lexington.
Dr. Modesitt is an associate professor, Gynecologic Oncology, University of Virginia, Charlottesville.

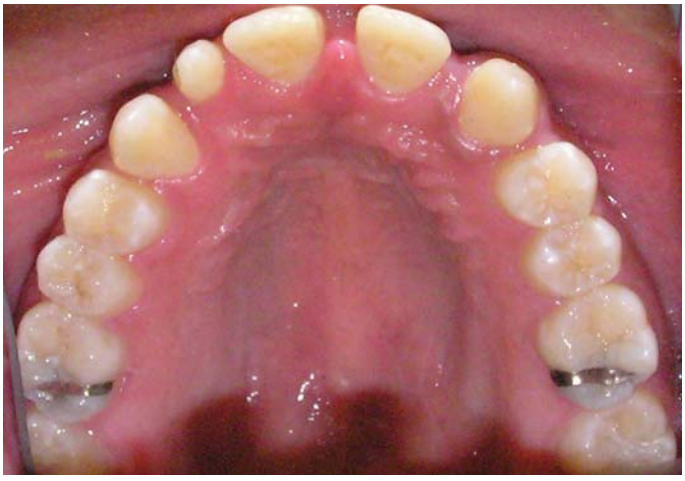

Figure. Hypodontia: lateral incisor agenesis and microdontia.

paired box 9 (*PAX9)* gene expression, which also is implicated in hypodontia, is correlated with increasing malignancy of dysplastic and cancerous epithelium of the human esophagus.[6]

Odontogenesis requires a complex orchestration of events for normal development, with known master regulatory genes being responsible for the spatial and temporal regulation of this process.[7,8] Disruption of these events can lead to hypodontia, which frequently is associated with other dental anomalies including microdontia (Figure), structural alterations, transpositions, delayed development and permanent canine impaction.[9,10] Structural alterations are thought to be incomplete expression of a genetic defect that otherwise would result in complete agenesis.[11]

The prevalence of hypodontia, excluding third molars, ranges from 2.6 to 11.3 percent, depending on the studied population. Females are affected more than males.[9,12,13] Mandibular second premolars are the most frequently affected teeth, and maxillary lateral incisors are the next most frequently affected teeth.[9,13] The severity of nonsyndromic hypodontia typically is mild; only one or two teeth are affected in the majority of patients.[9] Genetic linkage studies in families with hypodontia have identified mutations in several genes associated with some familial forms of hypodontia.[4,14,15] Autosomal dominant inheritance is the most common mode of transmission; however, autosomal-recessive and X-linked inheritance also have been reported.[11] In addition to these rare forms of hypodontia, which are associated with single gene mutations that show mendelian inheritance, multifactorial inheritance also has been implicated in hypodontia, with unknown genetic and environmental influences playing a role.[12]

Mutations in msh homeobox 1 (*MSX1)* and *PAX9* genes have been associated with familial, nonsyndromic forms of hypodontia.[14-22] The *MSX1* and *PAX9* genes encode transcription factors that are responsible for the spatial and temporal regulation of odontogenesis, particularly during the initiation and bud stage of development.[1,8,23-25] A novel mutation in the *AXIN2* gene has been identified as being involved in certain forms of familial tooth agenesis.[3,5] The *AXIN2* gene regulates the Wnt signaling pathway, which is involved in the cellular proliferation, differentiation and morphogenesis of most organs.[26,27] The roles of *MSX1, PAX9, AXIN2,* BARX homeobox 1 (*BARX1)* and BARX homeobox 2 (*BARX2)* genes in processes other than odontogenesis are being investigated.[26-31] For example, the link between the *AXIN2* gene and colon cancer has been described, and *AXIN2* genes also may play a role in ovarian cancer.

Ovarian cancer is the most fatal malignancy of the female genital tract, and there are no known early diagnostic markers or effective treatments. The American Cancer Society estimated that approximately 23,000 new cases of ovarian cancer would be diagnosed in the United States in 2007, resulting in more than 15,000 deaths.[32] Ovarian cancer accounts for about 3 percent of all cancers in women and typically is diagnosed in women 55 years or older. Ovarian cancer will be diagnosed in one in 67 women. Both inherited and acquired genetic mutations are implicated in this malignancy, as with most cancers. Approximately 10 percent of epithelial ovarian cancers (EOCs) are hereditary in origin, and mutations in the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) tumor suppressor genes are implicated in the majority of cases.[33] Other risk factors for EOC include hormonal or environmental alterations such as infertility, obesity, hormone replacement therapy, early menarche, late menopause, and tobacco and alcohol use.[32]

We conducted a study to establish and compare the prevalence rates of hypodontia among EOC

ABBREVIATION KEY. ***AXIN2:*** Axis inhibition protein 2. ***BARX1:*** BARX homeobox 1. ***BARX2:*** BARX homeobox 2. ***BRCA1:*** Breast cancer 1. ***BRCA2:*** Breast cancer 2. **EOC:** Epithelial ovarian cancer. ***MSX1:*** Msh homeobox 1. ***PAX9:*** Paired box 9. ***p53:*** p53 tumor suppressor. **Wnt:** Wingless type.

subjects and control subjects and to review possible genetic associations between these two phenotypes. We hypothesized that, if found, such an association could allow the clinical presentation of hypodontia to serve as a potential risk marker for EOC and, thus, enhance earlier detection and treatment of this lethal malignancy.

SUBJECTS, MATERIALS AND METHODS

Subjects. After we received approval from the University of Kentucky's institutional review board, we recruited 160 subjects and obtained informed consent from them. Fifty women from the Gynecologic Oncology Clinic at the University of Kentucky (Lexington) whose EOC had been diagnosed made up the sample population. One hundred women who had participated in the clinic's ovarian cancer screening program and who, as determined on the basis of their screening results, did not have ovarian cancer made up the control group. Ten women from the screening clinic had ovarian cysts, so we excluded them from the study. The women who participate in this ovarian cancer screening represent a general population of women and are not an unusually high-risk population for EOC.

Women with epithelial ovarian cancer are 8.1 times more likely to have hypodontia than are women without epithelial ovarian cancer.

Exclusionary criteria included premenopausal women, women with dentures, and women in the control with any ovarian abnormalities as assessed by transvaginal sonography. The clinic uses transvaginal sonogram technology to detect abnormal ovarian morphology, which generally is indicative of a cystic state or a potential malignancy. We did not exclude any racial ethnicities from the study. The examining dentist was not blinded to the ovarian cancer status of each subject.

Data collection. We reviewed each subject's medical and dental histories with her and recorded any family history of cancer, tooth agenesis or both. We conducted a dental examination of each subject to detect clinically tooth agenesis or obvious structural alterations such as microdontia. The criteria we selected for a hypodontia phenotype included agenesis and microdontia. We reviewed radiographs and other diagnostic records and sought input from the appropriate general dentist in cases that were not otherwise evident. We excluded third molars from the study.

Statistical analysis. We determined the difference in prevalence rates of hypodontia between the EOC group and the control group by using the Fisher exact test with an established P value of $\leq .05$ as a standard for statistical significance. We calculated the crude odds ratio (OR) and associated 95 percent confidence interval (CI) for the EOC subjects with hypodontia versus the control subjects with hypodontia. We determined an age-adjusted OR by using a logistic regression model. We used two-sample t tests to compare the subjects' ages between the two groups. We used descriptive statistics to disclose the most frequently affected teeth.

RESULTS

The prevalence of hypodontia was 20 and 3 percent for the EOC and control subjects, respectively (Table 1). The difference between these two hypodontia rates was significant (Fisher exact test, $P < .001$). The data also showed that the crude OR was 8.1 (95 percent CI, 2.1-30.9), which implied that women with EOC are 8.1 times more likely to have hypodontia than are women without EOC. Maxillary lateral incisors, followed by second premolars, were the most frequently missing teeth; however, other presentations of hypodontia were seen (Table 2). The range of severity of hypodontia was similar between the two groups, with one to two teeth being affected per person.

Table 1 shows descriptive statistics for age and race among all subjects. The subjects in the control group were 7.4 years older than were the subjects in the EOC group (two-sample t statistic, $P = .0000055$). After adjusting for age, we found that the odds of hypodontia occurring was 6.9 times more in EOC subjects than in control subjects ($P = .01$; 95 percent CI, 1.6-29.7).

Twenty-two percent of EOC subjects reported having a family history of hypodontia compared with only 2 percent of the control subjects (Fisher exact test, $P < .001$). Twenty-eight percent of the EOC subjects reported having a family history of ovarian cancer compared with 9 percent of the control subjects (Fisher exact test, $P = .0031$). Table 3 shows descriptive comparisons between EOC subjects with hypodontia (n = 10) and control subjects (n = 3) with hypodontia. The mean

TABLE 1

Descriptive statistics and prevalence values for the study population.

VARIABLE	EOC* SUBJECTS (n = 50)	CONTROL SUBJECTS (n = 100)	*P* VALUE
Mean Age (Years) ± SD†	55.1 ± 12.7	62.5 ± 8.1	.0000055‡
Race (No.) **White** **African-American** **Hispanic** **Asian**	 49 0 0 1	 96 2 1 1	.87
Prevalence of Hypodontia (%)	20	3	.001‡
Severity of Hypodontia (No. of Teeth)	1-2	1-2	NA§
Most Frequently Affected Teeth	Maxillary lateral incisors, second premolars	Maxillary lateral incisors, second premolars	NA
Family History of Hypodontia (%)	22	2	.0001‡
Family History of Ovarian Cancer (%)	28	9	.0031‡

* EOC: Epithelial ovarian cancer.
† SD: Standard deviation.
‡ Statistically significant.
§ NA: Not applicable.

TABLE 2

Description of hypodontia among control subjects and subjects with EOC*.

SUBJECT	DESCRIPTION OF HYPODONTIA (TOOTH NO.)
CONTROL 1	Agenesis (6)
CONTROL 2	Microdontia (7 and 10)
CONTROL 3	Agenesis (20 and 29)
EOC 1	Agenesis (13) and microdontia (10)
EOC 2	Agenesis (20)
EOC 3	Microdontia (14 and 15)
EOC 4	Agenesis (7) and microdontia (10)
EOC 5	Agenesis (13)
EOC 6	Agenesis (7 and 10)
EOC 7	Microdontia (2 and 3)
EOC 8	Agenesis (7 and 10)
EOC 9	Agenesis (4)
EOC 10	Agenesis (7)

* EOC: Epithelial ovarian cancer.

age of the control subjects with hypodontia was 15.6 years older than that of EOC subjects with hypodontia (two-sample, *t* statistic *P* = .021). Sixty percent of EOC subjects with hypodontia reported having a family history of hypodontia compared with zero percent of control subjects with hypodontia (Fisher exact test, *P* = .19). Thirty percent of EOC subjects with hypodontia reported having a family history of ovarian cancer compared with zero percent of control subjects with hypodontia (Fisher exact test, *P* = .53).

DISCUSSION

Dental clinicians should be cognizant of molecular interrelationships that encompass the body as a whole. An appreciation of the complex interaction of a person's genetic makeup and the outward, or phenotypic, expression of that array can help us, as health care providers, understand what may be occurring in the body and what could occur in the future.

Genetic alterations in key regulators of development can have many phenotypic consequences. The findings from our study support a possible association between two phenotypes: hypodontia and EOC. To have a greater understanding of a possible phenotypic association, molecular analysis of the genes of interest is necessary.

It is plausible to think that if a person had a mutation in a key regulator of embryonic development and cellular maintenance, specifically the *MSX1, PAX9* or *AXIN2* genes, hypodontia may be detected early in life. The same genetic mutation, however, may result in the development of cancer, which would not be detected until later in life. Therefore, hypodontia has the potential of becoming a risk marker for future cancer development.

We found that there was a strong family history of hypodontia in the EOC subjects. This finding may further implicate the potential asso-

ciation between these two conditions. Two of the EOC subjects reported having granddaughters who had the more severe form of hypodontia, known as oligodontia, in which more than six permanent teeth were missing. Familial studies, in which large kindreds are recruited, could add insight into possible genetic similarities between dental and ovarian abnormalities. Although 10 percent of ovarian cancer is familial and the majority of the inherited types are related to mutations in the *BRCA1* and *BRCA2* genes,[33] other unknown genetic mutations may play a crucial role.

TABLE 3

Descriptive statistics for subjects with hypodontia.

VARIABLE	EOC* SUBJECTS (n = 10)	CONTROL SUBJECTS (n = 3)	*P* VALUE
Mean Age (Years) ± SD†	49.7 ± 11.3	65.3 ± 3.1	.021‡
Race (No.)			> .99
White	9	3	
African-American	0	0	
Hispanic	0	0	
Asian	1	0	
Family History of Hypodontia (%)	60	0	.19
Family History of Ovarian Cancer (%)	30	0	.53

* EOC: Epithelial ovarian cancer.
† SD: Standard deviation.
‡ Statistically significant.

The results of our study indicate a possible molecular link between hypodontia and EOC. The possible molecular similarities between hypodontia and cancer may lie within specific genes (Table 4). The *MSX1, PAX9* and *BARX1* and *BARX2* genes are considered homeobox or master regulatory genes, while the *AXIN2* gene functions in biological signaling pathways. All of these genes are key regulators of developmental patterning, and their full expression typically is maintained in adult tissues in which cell growth, proliferation and differentiation requires control, thus implicating a fine balance between organogenesis and cancer.[29]

The *MSX1* gene, which is implicated in nonsyndromic hypodontia, is a regulator of the p53 tumor suppressor gene (*p53)* and is essential for the stabilization, nuclear accumulation and apoptotic function of *p53*.[30] Park and colleagues[31] showed that the *MSX1* gene also functions as a potential repressor of cell cycle progression in human ovarian cancer cell lines.

Mutations of the *PAX9* gene have been associated with certain forms of sporadic and familial forms of hypodontia. To date, no studies have been performed that evaluate whether *PAX9* gene

TABLE 4

Genes possibly implicated in hypodontia and ovarian cancer.

GENE (SYMBOL)*	FUNCTION	MUTANT PHENOTYPE	REFERENCE NOS.
Msh homeobox 1 (*MSX1*)	Odontogenesis; regulator of p53 tumor suppressor gene; repressor of cell proliferation in ovarian cancer	Selective tooth agenesis; ovarian cancer	1,2,15,17,18, 21-25,30,31
Axis inhibition protein 2 (*AXIN2*)	Odontogenesis; tumor suppressor gene	Selective tooth agenesis; colon and ovarian cancer	3-5,26,27
BARX homeobox 1 (*BARX1*) and BARX homeobox 2 (*BARX2*)	Expressed in craniofacial structures during development; transcriptional regulator of cell adhesion molecules; possible tumor suppressor roles in epithelial ovarian cancer	Decreased levels of expression in certain forms of epithelial ovarian cancer; not yet implicated in hypodontia	36,37
Paired box 9 (*PAX9*)	Odontogenesis; maintaining cellular differentiation of esophageal keratinocytes	Selective tooth agenesis; squamous cell carcinoma of the human esophagus	6,14,16,19-22

* Listed by importance with regard to an association between epithelial ovarian cancer and hypodontia.

mutations are involved in EOC development or progression. Gerber and colleagues,[6] however, have correlated a loss or reduction of *PAX9* gene expression in the increasing severity of dysplastic and cancerous epithelium of the human esophagus.

The *AXIN2* gene, which is involved in odontogenesis and hypodontia, functions as a regulator of the Wnt signaling pathway, which is responsible for controlling the cellular proliferation, differentiation and morphogenesis of most organs.[26,27] Alterations in the Wnt signaling pathway result in an unbalanced cellular homeostasis, which plays a prominent role in the pathogenesis of many human cancers.[3,26] Mutations in the *AXIN2* gene have been linked to a specific form of EOC, known as ovarian endometrioid adenocarcinoma, through deregulation of the Wnt signaling pathway.[34,35] Another study has shown an association between familial tooth agenesis and colorectal cancer via a mutation in the *AXIN2* gene.[3]

The *BARX1* and *BARX2* genes are expressed in the maxillary and mandibular arches during embryonic development in areas of epithelial-mesenchymal interactions,[36] thus implicating that the *BARX1* and *BARX2* genes may have a role in odontogenesis. There are no studies thus far linking *BARX1* and *BARX2* gene mutations to hypodontia. Sellar and colleagues[37] found that the *BARX2* gene is expressed in normal ovarian surface epithelium and acts as a transcriptional regulator of the cadherin 6 gene (also known as *CDH6*) and other cell adhesion molecules. They also showed that the expression of the *BARX2* gene is significantly lower in certain groups of EOC cell lines, specifically endometrioid and clear cell. In vitro results showed that transfection of the *BARX2* gene into an ovarian cancer cell line that does not endogenously express the *BARX2* gene correlated with a suppressor role in ovarian cancer cell invasion, migration and adhesion.

Our findings should be considered within the limitations of our study. Our protocol included reliance on patients' histories and dental records to diagnose missing teeth. The examining dentist was not blind to the ovarian cancer status of each subject, thus allowing for an area of potential bias in the study design. Moreover, a sample size of 50 experimental subjects is relatively small. The significance of our findings, however, justifies a comprehensive follow-up study that includes genetic analysis to explore possible genetic similarities between hypodontia and EOC.

Our research along with more broad-scale studies could pave the way for earlier and more consistent ovarian cancer screening regimens for women who have hypodontia. Such a simple modification in the screening process could aid in preventing fatal outcomes, which often are associated with late diagnosis of this inconspicuous malignancy.

CONCLUSIONS

We observed a statistical association between hypodontia and EOC that warrants further investigation into a possible molecular association between these two conditions. For example, the prevalence of hypodontia was significantly greater in women with EOC (20 percent) than in women without EOC (3 percent) ($P < .001$). The crude OR was 8.1 (95 percent CI, 2.1-30.9), suggesting that women with EOC are 8.1 times more likely to have hypodontia than are women without EOC. ■

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