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# A Systematic Review of case Reports of Neoplastic Changes in Epithelial lining of Dentigerous Cysts

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## ABSTRACT

Introduction: The possibility of transformation of the epithelium lining the cavity of dentigerous cyst to a neoplastic one has been recognized for a number of cases, but it is difficult to establish that such an event has actually occurred. So, the current review aims to implement a systematic review to identify the potential demographic, clinical and radiological characteristics of the malignant transformation that arose in DC. Material and method: The review was carried out per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). 50 articles were reviewed and reported 55 cases with neoplastic changes originated from dentigerous cysts. Result: The demographic and clinical characteristics of the included cases showed that the mean age of the affected patients was 44.04 ±23.36 years, ranged from 1.33 to 84 years. Thirty-three patients (60%) were males. Most of the reported neoplasms were in mandible (72.7%). Primary sites of these neoplasms were the posterior regions (35, 63.6%), with majority of cases recorded in molar areas (26, 47.3%), while the incisor region affected less frequently (5, 9.1%). Radiographically, the majority of neoplasm appeared as unilocular radiolucency (39, 70.9%), while multilocular radiolucency reported in 2 cases only (3.6%). Histopathologically, malignant transformations were noticed in 40 cases (72.7%) and the majority of them were squamous cell carcinoma (35, 63.6%) mostly of well differentiated type (25, 45.5%), provided that 20 cases (36.4%) were not described regarding histological differentiation. On the other hand, adenomatoid odontogenic tumor represented as most benign lesion associated with the dentigerous cyst (10, 18.2% of all neoplasms and 66.7% of the benign lesions). Most of the neoplasm cases were reported in India (19, 34.5%) and were of Asian race (26, 47.3%). Conclusion: Although most studies report that neoplastic transformation rarely occurs in the lining of the dentigerous cyst but unfortunately, the malignancies occur with higher frequency than do the benign tumors.

***Keywords:*** dentigerous, cyst, malignant, systematic reviews, meta-analyses.

## 1 Introduction

The dentigerous cyst (DC) is the most common type of developmental odontogenic cysts. DC originates around an unerupted tooth by the separation of the follicle from around the crown at cementoenamel junction. Although its pathogenesis is uncertain, experts believe that it develops due to accumulation of fluid between the reduced enamel epithelium and the tooth crown. In an ascending order of frequency, this type of cysts involves mandibular third molars, maxillary canines, maxillary third molars and mandibular second premolars.

Small DC is mostly asymptomatic and diagnosed coincidentally in jaws/head radiographs that taken for other reason in patients aged between 10-30 years with evident predilection to males. When large, although not common, DC may cause painless expansion of the bone in the affected area that may result in facial asymmetry. Although DC has benign nature and excellent prognosis, there is a very low possibility that its lining might undergo neoplastic transformation [1-3].

The epithelial lining of an odontogenic cyst rarely gives rise to benign odontogenic tumor like ameloblastoma and adenomatoid odontogenic tumor. Mucoepidermoid carcinoma and squamous cell carcinoma (SCC) have been reported to arise in pre-existing DC [4, 5].

Despite the huge studies on oncogenesis, transformation of a sound cell to a neoplastic one remains a challenge. The scenario is applied to DC; no sound evidence has been available so far. However, the possibility of chronic inflammation-induced carcinogenesis should be taken into consideration [6- 8]. In addition, damage of DNA, apoptosis of normal cells, insertion of oncogenes and immunosuppression have been postulated as potential causes of malignant transformation [9- 16].

In light of scarcity of data on the characteristics and potential risk factors of neoplastic transformation of DC, this study's aim was to implement a systematic review to identify the potential demographic, clinical and radiological characteristics of the neoplastic changes that arose in DC.

## 2 Material and Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [12]. 50 articles were reviewed and reported 55 cases with neoplastic changes originated from dentigerous cysts.

### 2.1 *Focused question*

The clinical research question was: What demographic, clinical and radiological features that reported in cases of neoplastic lesions arose in DC?

### 2.2 *Search strategy*

The search strategy retrieves all pertinent case reports and/or case series published from inception in 1958 till March 2016 . The electronic search and the PICO criteria are shown in Table 1.

### 2.3 *Inclusion criteria*

The following inclusion criteria were adopted in accordance with the PICO criteria [17]:

- population (P): patients with DC confirmed clinically and histopathologically.
- intervention (I): confirmed neoplastic changes derived from epithelial lining of DC.
- control (C): not applicable.
- outcome (O): an incidence of malignant transformation derived from the lining of DC.
- study design (S): Clinical human studies, including cohort studies (retrospective or prospective), case reports and case series that reported neoplastic changes arising in/from the lining of DCs and confirmed by histopathological examination were included.

### 2.4 *Exclusion criteria*

The following exclusion criteria were applied:

(1) technical reports.
(2) animal or in vitro studies.
(3) studies that did not report the histopathological confirmation of DC.
(4) the presence of neoplastic changes belonging to metastasis from distant primary tumors.
(5) studies that did not sufficiently specify the type of odontogenic cysts.
(6) studies that did not report a detailed follow-up.
(7) studies that did not report enough clinical and histopathological evidence to confirm the diagnosis of neoplastic changes from the epithelial lining of DCs.

### 2.5 *Data extraction*

Data were extracted independently by two researchers (EA and AH) using a specially prepared data extraction form. The following data were extracted from each study: authors, year, study design, male to female ratio, age (average), number of patients, location of lesions, clinical and radiographic features, histopathological diagnosis, type of neoplastic changes, nationality and ethnicity.

### 2.6 *Quality assessment of the studies included*

Because all of the articles included were case reports, critical appraisal was not performed.

### 2.7 *Statistical analysis:*

The available data were patient's gender, age, nationality and race; Jaw, tooth and site involved; radiographic features; neoplasm type (benign or malignant); and histopathologic diagnosis and differentiation. Apart from age, which was presented as mean and standard deviation, the other variables were categorical and described as frequencies and proportions. The potential differences in age between

different subgroups were assessed by independent t-test or one-way ANOVA, as appropriate. The potential associations between different categorical factors were evaluated using Chi square test. A *P* value of < 0.05 was considered significant. All analyses were conducted using SPSS version 21 (IBM Corp., Armonk, NY, USA).

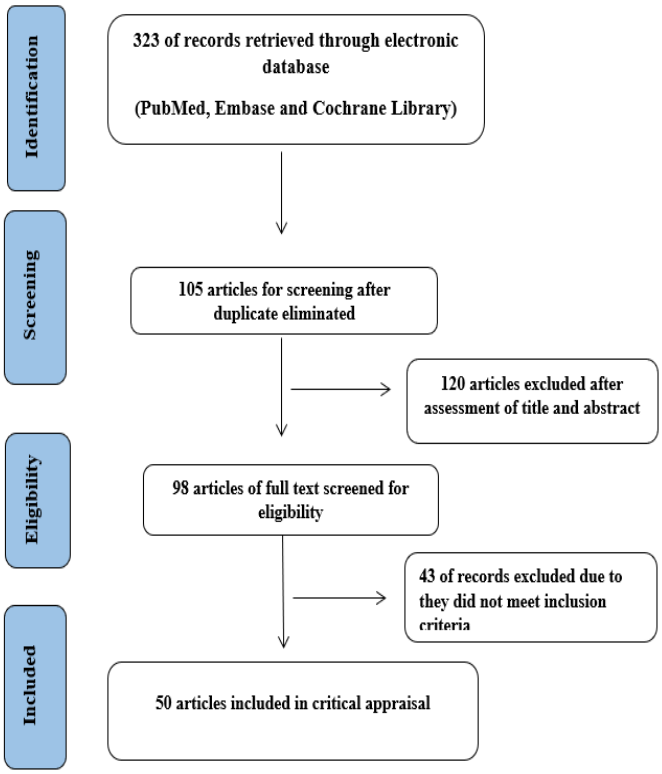


**Fig. 1.** Selecting screening process

## 3 *Results*

The current work reviewed 50 published papers that reported 55 cases with neoplastic changes originated from dentigerous cysts during the period from 1980 1958 to March 2016. The demographic and clinical characteristics of the included cases are presented in table 1. The mean age of the affected patients was 44.04 ±23.36 years, ranged from 1.33 to 84 years. Thirty-three patients (60%) were males with a male to female ratio of 1.5:1. Most of the reported neoplasms were in mandible (72.7%) with a mandible to maxilla ratio of 2.7:1. Primary sites of these neoplasms were the posterior regions (35, 63.6%), with majority of cases recorded in molar areas (26, 47.3%), while the incisor region affected less frequently (5, 9.1%).

Radiographically, the majority of neoplasm appeared as unilocular radiolucency (39, 70.9%), while multilocular radiolucency reported in 2 cases only (3.6%). Histopathologically, malignant transformations were noticed in 40 cases (72.7%) and the majority of them were squamous cell carcinoma (35, 63.6%) mostly of well differentiated type (25, 45.5%), provided that 20 cases (36.4%) were not described regarding histological differentiation. On the other hand, adenomatoid odontogenic tumor represented as most benign lesion associated with the dentigerous cyst (10, 18.2% of all neoplasms and 66.7% of the benign lesions). Most of the neoplasm cases were reported in India (19, 34.5%) and were of Asian race (26, 47.3%).

**TABLE 1.** Summary of the characteristics of the included cases

| Factor | Subgroups | N (%) |
|---|---|---|
| Gender | Male | 33 (60) |
| | Female | 22 (40) |
| Jaw | Mandibular | 40 (72.7) |
| | Maxilla | 15 (27.3) |
| Tooth/teeth | Incisor | 5 (9.1) |
| | Canine | 13 (23.6) |
| | Premolar | 9 (16.4) |
| | Molar | 26 (47.3) |
| | NS | 2 (3.6) |
| Site | Anterior | 18 (32.7) |
| | Posterior | 35 (63.6) |
| | NS | 2 (3.6) |
| Radiographic features | Diffuse radiolucency | 2 (3.6) |
| | Ill-defined radiolucency | 2 (3.6) |
| | Irregular radiolucency | 5 (9.1) |
| | Multilocular radiolucency | 2 (3.6) |
| | Unilocular radiolucency | 39 (70.9) |
| | Well-defined radiolucency | 3 (5.5) |
| | Radiolucency | 1 (1.8) |
| | NS | 1 (1.8) |
| Histopathological | Adenomatoid odontogenic tumor | 10 (18.2) |
| | Ameloblastoma | 5 (9.1) |
| | Carcinoma in situ | 1 (1.8) |
| | Mucoepidermoid carcinoma | 3 (5.5) |
| | Squamous cell carcinoma | 35 (63.6) |
| | Verrucous carcinoma | 1 (1.8) |
| Type of neoplasm | Benign | 15 (27.3) |
| | Malignant | 40 (72.7) |
| Differentiation | Well | 25 (45.5) |
| | Moderate | 9 (16.4) |
| | Poor | 1 (1.8) |
| | NS/NA | 20 (36.4) |
| Country | Brazil | 1 (1.8) |
| | Canada | 1 (1.8) |
| | China | 1 (1.8) |
| | Germany | 1 (1.8) |
| | India | 19 (34.5) |
| | Japan | 4 (7.3) |
| | Netherlands | 1 (1.8) |
| | Nigeria | 1 (1.8) |
| | Poland | 1 (1.8) |

| | | |
|---|---|---|
| | Spain | 4 (7.3) |
| | Russoia | 1 (1.8) |
| | Taiwan | 2 (3.6) |
| | Thailand | 1 (1.8) |
| | UK | 4 (7.3) |
| | USA | 10 (18.2) |
| | NS | 3 (5.5) |
| Race | Asian | 26 (47.3) |
| | Caucasian | 24 (43.6) |
| | Black | 2 (3.6) |
| | NS | 3 (5.5) |
| Age: Mean (SD), Range in years (N = 55) | | 44.04 (23.36), 1.33-84 |

Clinically, the majority of cases complained initially of swelling (29=52.7%), or pain (8=14.5%). There were 18 cases (32.7%) complaining other than mentioned above; eight of them (14.5% of all cases) had asymptomatic lesions. The detailed complaints associated with the cases included are presented in table 2.

**TABLE 2.** Summary of the clinical features of the included cases.

| Main clinical features | Associated features | N (%) |
|---|---|---|
| Pain (N =8; 14.5%) | Pain only | 4 (7.3) |
| | Pain and swelling and fistula | 1 (1.8) |
| | Pain and swelling and tooth mobility | 1 (1.8) |
| | Pain on mouth opening | 1 (1.8) |
| | Tingling pain | 1 (1.8) |
| Swelling (N = 29, 52.7%) | Swelling only | 15 (27.3) |
| | Swelling and discomfort | 2 (3.6) |
| | Swelling and pain | 7 (12.7) |
| | Swelling and pain and trismus | 1 (1.8) |
| | Swelling and pain and parasthesia | 1 (1.8) |
| | Swelling and facial asymmetry | 1 (1.8) |
| | Swelling with nasal obstruction | 1 (1.8) |
| | Swelling with pus discharge | 1 (1.8) |
| Others (N = 18, 32.7%) | Asymptomatic | 8 (14.5) |
| | Discomfort | 2 (3.6) |
| | Extraction of impacted tooth | 1 (1.8) |
| | Fistula after extraction | 1 (1.8) |
| | Ill-fitting denture | 2 (3.6) |
| | Nasal obstruction | 1 (1.8) |
| | Recurrent infection and numbness | 1 (1.8) |
| | Trismus | 1 (1.8) |
| | Un-erupted tooth | 1 (1.8) |

The affected males were older than females (51.24±20.4 vs. 33.24±2379, P = 0.004). Cases affected by malignant neoplasms were older than their counterparts (52.7±21.1 vs. 20.93±9.1, P < 0.001). Similarly, cases who complained about pain and those of Caucasian race were older than their counterparts (P = 0.039 and 0.031, respectively, table 3).

**TABLE 3.** Mean age by different grouping factors.

| Factor | Subgroups | Age (Yrs) | P value |
|---|---|---|---|
| Gender | Male (n = 33) | 51.24 (20.4) | 0.004 |
| | Female (n = 22) | 33.24 (23.79) | |
| Type of neoplasm | Malignant (n = 40) | 52.71 (21.07) | < 0.001 |
| | Benign (n = 15) | 20.93 (9.07) | |
| Main clinical features | Pain (n = 8) | 50.13 (21.06) | 0.039 |
| | Swelling (n = 29) | 36.6 (23.95) | |
| | Others (n = 18) | 53.33 (20.07) | |
| Ethnicity | Asian (n = 24) | 37.19 (23.38) | 0.031 |
| | Caucasian (n = 26) | 49.81 (19.56) | |
| | Black (n = 2) | 15.5 (14.85) | |

Most of included females (77.3%) complained swelling in comparison to 42.4% of males who complained signs and symptoms other than pain and swelling (P = 0.011). Up to 88% of males developed malignant neoplasms compared to 50% of females (P = 0.02). Most of the affected males were Caucasians (61.3%) compared to 71.4 females who were Asians (P = 0.028, Table 4).

**TABLE 4.** Associations of gender with different grouping factors.

| Factor | Subgroups | Males | Females | P value |
|---|---|---|---|---|
| Main clinical features | Pain (n = 8) | 7 (21.2) | 1 (4.5) | 0.011 |
| | Swelling (n = 29) | 12 (36.4) | 17 (77.3) | |
| | Others (n = 18) | 14 (42.4) | 4 (18.2) | |
| Type of neoplasm | Malignant (n = 40) | 29 (87.9) | 11 (50) | 0.002 |
| | Benign (n = 15) | 4 (12.1) | 11 (50) | |

| | | | | |
|---|---|---|---|---|
| Ethnicity | Asian (n = 24) | 11 (35.5) | 15 (71.4) | 0.028 |
| | Caucasian (n = 26) | 19 (61.3) | 5 (23.8) | |
| | Black (n = 2) | 1 (3.2) | 1 (4.8) | |

The neoplasms were reported more frequently in posterior area of the mandible (81.1%) while they were reported more frequently in the anterior area of the maxilla (78.6%) compared to the other jaw areas (P < 0.001). In addition, most of the mandibular neoplasms were malignant (80%) while those of maxilla were benign (53.3%, P = 0.048). The molars were the most affected teeth in mandible (61.5%) compared to canines in maxilla (57.1%, P < 0.001). Caucasians had the highest proportion of mandibular involvement (56.4%) while Asians revealed the highest maxillary involvement (84.6%, P = 0.015, table 5).

**TABLE 5.** Associations of the affected jaw with different grouping factors.

| Factor | Subgroups | Mandibular | Maxilla | P value |
|---|---|---|---|---|
| Site | Anterior (n = 18) | 7 (17.9) | 11 (78.6) | < 0.001 |
| | Posterior (n = 35) | 32 (81.1) | 3 (21.4) | |
| Tooth | Incisor (n = 5) | 2 (5.1) | 3 (21.4) | 0.001 |
| | Canine (n = 13) | 5 (12.8) | 8 (57.1) | |
| | Premolar (n = 9) | 8 (20.5) | 1 (7.1) | |
| | Molar (n = 26) | 24 (61.5) | 2 (14.3) | |
| Type of neoplasm | Malignant (n = 40) | 32 (80) | 8 (53.3) | 0.048 |
| | Benign (n = 15) | 8 (20) | 7 (46.7) | |
| Ethnicity | Asian (n = 24) | 15 (38.5) | 11 (84.6) | 0.015 |
| | Caucasian (n = 26) | 22 (56.4) | 2 (15.4) | |
| | Black (n = 2) | 2 (5.1) | 0 (0) | |

## 4 *Discussion:*

The current study reviewed 50 published papers that reported 55 cases with neoplastic changes originated from dentigerous cysts from 1958 to March 2016. Although exceedingly rare, development of neoplastic changes in the lining of an odontogenic cyst does occur. The etiopathogenesis of such changes is uncertain [1-45]. However, many experts postulated inflammation and/or infections as a driving cause [46, 47]. It is argued that the longstanding inflammatory process predisposes to neoplastic changes in the lining of the cyst [48, 49]. This is supported by the fact that the connective tissues of the lining of most of the neoplastic-transformed cysts are densely infiltrated by lymphocytes and plasma cells [50]. In addition, neoplastic transformation occurs more frequently in radicular and/or residual cysts [46, 51] which well-known they are induced by longstanding inflammations. Typically, the reactive oxygen and nitrogen species are liberated with chronic inflammation with the potential to damage DNA, proteins, and cell membranes, and to modulate enzyme activities and gene expression, resulting ultimately in carcinogenesis.

In addition, chronic inflammation may lead to apoptosis of normal cells resulting in a compensatory proliferative response by the remaining cells. These dividing cells are subject to DNA damage with a higher chance of growth of malignant cells [46]. However, this scenario explains part of the scene; few of the reported cases that diagnosed in children were inflammation-free [10-19]. Hence, the role of other, non-inflammatory factors, such as genetics [52, 53], should not be overlooked. In a recent study, the relationship between the epidermal growth factor receptor distribution in pericoronal follicles and the origin of odontogenic cysts and tumors has been proven [53]. Unlike cited elsewhere [16][44], most of the reported neoplastic changes in dentigerous cysts were malignant (40; 73%) in comparison to the benign changes (15; 27%). It is uncertain whether the incidence rates of these changes are truly different or might be attributed to publication bias; i.e., it can be postulated that authors/editors tend to publish the more dangerous entities (malignant changes) rather than publishing benign diseases. In line with that, the benign lesions included in this review (ameloblastoma and adenomatoid odontogenic tumor [AOT]) are ordinarily more frequent in maxillofacial pathology/surgery practice than the diagnosed malignant lesions (PIOSCC and CMEC) and this further explains the higher rate of publication of the latter.

Moreover and unlike PIOSCC, no clear-cut criteria have been in-use to differentiate the cystic variant of AOT and hence it might be under-reported (29). On the other hand, three types of PIOSCC have been described:

- a solid tumor that invades marrow spaces and induces osseous resorption.
- squamous cancer arising from the lining of an odontogenic cyst
- a squamous cell carcinoma in association with other benign epithelial odontogenic tumors.

For the PIOSCC that arises from the lining of an odontogenic cyst, there may be a histological transition between the carcinoma and the benign precursor. This is an essential criterion to confirm the cystic origin of the carcinoma [54]. In this review, we included studies that diagnosed type 2 PIOSCC based on presence of such a transition in addition to other clinical and radiographic characteristics that confirm the occurrence of malignant transformation in a preexisting dentigerous cyst. However, identification of such a transition in more advanced stages

can be difficult [44]. Most of the reported cases were males (60% vs. 40%) representing a male to female ratio of 1.5:1 which reflects the gender incidence of the dentigerous cyst (55). When considered separately, the male to female ratio for malignant transformation was 2.6:1, while it was 0.36:1 for benign transformation. Such a male predilection toward malignant transformation can be attributed partially to the higher incidence of dentigerous cyst in males. But why there is a female predilection to benign transformation? Indeed, most of the benign transformation were adenomatoid odontigenic tumor (8 out of 10) which is classically more common in females [29]. This raises question marks whether these reported adenomatoid odontigenic tumors originated from preexisting dentigerous cysts, they were misdiagnosed as such, or were coincidentally present. Hence, the conception of "benign transformation of dentigerous cysts" is questionable. Interestingly, the mean age of the reported cases varied significantly by the neoplastic type. Patients with malignancies were older (52.71±21.07 years) than cases with benign tumors (20.93±9.07 years). In one large study, the average age of patients with dentigerous cysts was 35±17 years and this is 15 years later than the reported benign cases and 16 years earlier than the malignant cases. It can be argued that the malignant transformation may take years to occur in dentigerous cyst.

However, what about the occurrence of benign transformation 15 years earlier to the time of peak incidence of the dentigerous cyst? Again this raises question marks with regard to the cystic origin of the reported benign tumors. But, apart from the average age which is around 3rd decade, there is a wide variation in age distribution ranging from 6 to 99 years and this cannot be overlooked [55]. Similarly, males were significantly older (51.24±20.4 years) than females (33.24±23.79 years). This might be a misleading result. In fact, most of the reported malignancies were in males in comparison of females. Hence, such a difference in age is really attributed to the type of neoplasia, as pointed above, rather than to gender. Apart from the neoplasm type, most of the included cases were reported in mandible (39 cases) specifically in the posterior area (32 cases) and more specifically in the molar region (24 cases). This evidently reflects the distribution of the origin of these neoplasms (dentigerous cyst) [55].

On the other hand, most of the reported cases in the maxilla were in the anterior area (11 cases) specifically in the canine region (8 cases). This may indicate that the risk of neoplastic transformation of the dentigerous cyst is higher in the anterior maxilla which is affected by this type of cyst less frequently than the posterior maxilla [55, 56]. Otherwise, the distribution of these cases in maxilla mimics to large extent the distribution of the benign odontogenic tumors in this jaw. Considering "type of neoplasm", there were 32 malignancies reported in the mandible in contrast to only 8 cases in the maxilla. Eight benign tumors were reported in the mandible versus seven in the maxilla. This further stresses the jaw distribution of the original lesion (dentigerous cyst). In addition, such results showed a higher tendency toward malignancy development in dentigerous cysts of the mandible in contrast to an equal potential risk of developing malignant and benign tumors in dentigerous cysts of the maxilla. The latter result cannot be explained and needs further confirmation and research. Classically, most dentigerous cysts are asymptomatic and discovered incidentally on routine radiographs. Some dentigerous cysts, however, may grow to considerable size and produce bony expansion that is usually painless, unless secondarily infected [57]. In this review, only 8 cases were asymptomatic while the most common complaint was swelling with or without pain (29; 52.7%). Pain alone was reported in 4 cases and in other 4 cases pain was associated with other complaints. It is the nature of neoplasia to cause enlargement (swelling); when malignant, it invades the surrounding structures causing pain. Hence, any cystic lesion should be planned for immediate treatment when causing swelling, pain or both.

## 5 *Conclusion*

Within the limitations of the current review, it can be concluded that neoplastic transformation rarely does occur in the lining of the dentigerous cyst. Unfortunately, the malignancies occur with higher frequency than do the benign tumors; the former are diagnosed at 5th decade averagely with evident tendency toward males.

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**Financing:** The study was performed without external funding.
**Ethical consideration:** The study was approved by Ibn Sina *University*, Babylon Iraq.

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