

Supplementary Material

Feline Oral Squamous Cell Carcinoma: A Critical Review of Etiologic Factors

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Table S1. Grading system used to score the quality of experimental design for manuscripts included in this systematic review, modified from a grading system published by the Oxford Centre for Evidence-based Medicine.

| Experimental design grade (EDG) | Study types |
|---------------------------------|--|
| I | Randomized, controlled, double-blinded prospective clinical trials |
| II | Prospective clinical trials |
| III | Retrospective case series, (n > 10) |
| IV | Retrospective case series (n < 10) |
| V | Single patient case report; expert opinion |

Table S2. Data collection related to viruses.

| Reference | Geographic location | Level of evidence | Cats with FOSCC (n) | Breed (n) | Gender (n) | Animals' lifespan (n) | Virus (% positive) | Diagnostic test |
|-------------------------------------|---------------------|-------------------|---------------------|-------------------------------|----------------------------|---|---|---|
| Chu <i>et al.</i> , 2019 [34] | USA | III | 20 | ND | M (10) F (10) | AdMa (8) G (12) | FcaPV-3 (5%) FFV (35%) FTTV (10%) EBV (5%) FHV-1 (10%) FeLV (0%) FIV (0%) | ViroCap, PCR (only on EBV and FcaPV – 3 positive) |
| Gendler <i>et al.</i> , 2010[47] | USA | III | 18 | ES (14) H (2) MC (2) | M (7) F (11) | 13.2 ± 3.5 | FIV (0%) FeLV (0%) | Only referred sanitary status |
| Yamashita <i>et al.</i> , 2018 [32] | Japan | IV | 8 | ES (8) | M (4) F (4) | Sen (5) G (3) | FcaPV-2 (0%) FcaPV-3 (0%) FcaPV-4 (0%) | PCR; IHC p16 |
| Altamura <i>et al.</i> , 2020 [35] | Italy | III | 32 | ES (18) Per (1) SI (13) | M (6) F (15) ND (11) | Ad (1) AdMa (5) Sen (6) G (1) SI (19) | FcaPV-2 (31,3%) | PCR; IHC (only on PV-positive) |
| O'Neill <i>et al.</i> , 2011 [24] | USA | IV | 2 | ES (1) H (1) | M (1) F (1) | AdMa 1) G (1) | HVP-38 (25%) PV (25%) | PCR |
| Munday <i>et al.</i> , 2009 [29] | New Zealand | III | 20 | EC (1) SI (19) | ND | AdMa (1) ND (19) | PV (5%) | PCR |

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|------------------------------------|-------------|-----|-----------------|---|------------------|---|--------------------------------|--|
| Munday <i>et al.</i> , 2011 [30] | New Zealand | III | 30 | ND | ND | 12.8 | PV (0%) | PCR; IHC p16 |
| Altamura <i>et al.</i> , 2018 [27] | Italy | IV | 1 | EC (1) | ND | Sen (1) | FcaPV-2 (100%) | PCR; IHC p53 and E6AP |
| Munday <i>et al.</i> , 2015 [17] | New Zealand | III | 36 | ND | ND | AdMa (1) Ad (1) SI (34) | FcaPV-1 (2.8%) FcaPV-4 (0%) | PCR; IHC p16 (only on FcaPV-1 positive) |
| Munday <i>et al.</i> , 2019[23] | New Zealand | III | 52 | ND | M (32) F (20) | 13.5 | PV (0%) | IHC p16 and p53 and PCR (only on p16-positive) |
| Hoggard <i>et al.</i> , 2018 [33] | USA | IV | 1 | EC (1) | ND | Sen (1) | FcaPV-2 (0%) | PCR; ISH |
| Anis <i>et al.</i> , 2010[36] | USA | IV | 1 | ND | ND | ND | HVP-38 (100%) | PCR |
| Hutson <i>et al.</i> , 1991[72] | USA | IV | 18 ^a | ND | ND | ND | FIV (22.2%) | PCR |
| Supsavhad <i>et al.</i> , 2016[31] | USA | III | 43 | ES (37) H (3) S (1) Per (1) A (1) | M (16) F (27) | J (1) Ad (3) AdMa (5) Sen (20) G (13) | PV (0%) | IHC; PCR (only on p16-positive) |
| Olmsted <i>et al.</i> , 2016 [55] | USA | III | 35 | ES (31) Ab (1) B (1) MC (1) | M (16) F (19) | 14 | FIV (2.9%) | Only referred sanitary status |

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|------------------------------------|-------|-----|-----|--|------------------|---------|--|-------------------------------|
| Altamura <i>et al.</i> , 2016 [26] | Italy | IV | 1 | ES (1) | ND | Sen (1) | FcaPV-2 (100%) | PCR; IHC (p53 and pRb) |
| Altamura <i>et al.</i> , 2022 [37] | Italy | III | 113 | ES (113) | ND | ND | FcaPV-1 (6.2%) FcaPV-2(7.5%) FcaPV-3(5.3%) FcaPV-4(0.9%) FcaPV-5(1.8%) | PCR |
| Zaccone <i>et al.</i> , 2021 [73] | Italy | III | 100 | Ch (5) S (2) P (1) MC (1) K (1) ES (90) | M (46) F (54) | ND | FeLV (0%) FIV (8%) | Only referred sanitary status |

M – Male; F – Female; PV – Papillomavirus; IHC – Immunohistochemistry; PCR – Polymerase chain reaction; RT-PCR – Reverse transcription PCR; ISH – *in situ* hybridization; FcaPV – *Felis catus* papillomavirus; FFV – *Feline foamy virus*; FTTV – *Feline torque teno virus*; EBV – *Epsteinn-Barr virus*; FHV – Feline herpesvirus; FIV – Feline immunodeficiency virus; FeLV – *Feline Leukemia virus*; HPV – Human Papillomavirus; H – Himalayan; ES – European Shorthair; S – Siamese; A – Angorá; Pe – Persian; Ab – Abyssinian; B – Bengal; J – Júnior; Ad – Adult; AdMa – Adult Mature; Sen – Senior; G – Geriatric; ND – No data; USA – United States of America.^a – 18 cats with FOSCC without specific location.

Table S3. Data collection related to environmental tobacco smoke.

| Reference | Geographic location | Level of evidence | Cats with FOSCC (n) | Breed (n) | Gender (n) | Animals' lifespan (n) | Exposure to EST (% of animals; RR; <i>p</i>) |
|-----------------------------------|---------------------|-------------------|----------------------|--|------------------|--------------------------------|---|
| Bertone <i>et al.</i> , 2003 [14] | USA | III | 36 | ES (34) Purebred (2) | M (16) F (20) | AdMa (4) Sen (21) G (11) | E (36.1%; 2.3; 0.11) NE (61.1%; 1.0; -) |
| Snyder <i>et al.</i> , 2004 [12] | USA | III | 23 | ND | M (16) F (17) | ND | E (47.8%; 4.5; 0.19) NE (52.2%; 1.0; -) |
| Renzi <i>et al.</i> , 2019 [13] | Italy | III | 24 ^b (26) | ES (22) Ch (2) S (1) Per (1) | M (12) F (14) | 14.5 | E (25.0%; -; -) NE (75.0%; -; -) |
| Zaccone <i>et al.</i> , 2021[73] | Italy | III | 100 | Ch (5) S (2) P (1) MC (1) K (1) ES (90) | M (46) F (54) | ND | E (31%; -; -) NE (69%; -; -) |

ES – European Shorthair; Ch – Chartreux; S – Siamese; Persa – Persian; M – Male; F – Female; E – Exposed; NE – Not exposed; P – Positive; N – Negative; Ad – Adult; AdMa – Adult Mature; Sen – Senior; G – Geriatric; ND - No data; RR – Relative risk; *p* – significance level; USA – United States of America. ^b

Information about smoke exposure is only available in 24 out of 26 cats.

Table S4. Data collection related to oral comorbidities and other risk factors.

| Reference (author, year of publication) | Geograph ic location | Level of evidence | Cats with FOSCC (n) | Breed (n) | Gender (n) | Animals' lifespan (n) | Flea control product (% animals; RR, <i>p</i>) | Diet (% animals; RR; <i>p</i>) | Oral comorbidities (% animals; RR; <i>p</i>) | Other risk factors (% animals; RR; <i>p</i>) |
|--|-------------------------|----------------------|---------------------------|---------------------|------------------|--------------------------------|--|--|--|--|
| Bertone <i>et al.</i> , 2003 [14] | USA | III | 36 | ES (34) Pure (2) | M (16) F (20) | AdMa (4) Sen (21) G (11) | Never (38.9%; 1.0;-) Collar (36.1%; 5.3; 0.002) Shampoo (5.6%; 0.1; 0.011) Powder (13.9%; 1.7; 0.42) Spray (13.9%; 1.2; 0.81) | Dry (27.7%;1.0;-) Canned (55.5%; 3.6; 0.014) Dry and canned (16.7%; 2.2; 0.27) Canned tuna (41.7%; 4.7; 0.004) Table scraps (44.4%; 1.2; 0.87) Liver (2.8%; 0.3; 0.30) | Dental pathology (33.3%; 1.8; 0.18) | City (13.9%; 0.4; 0.067) Small town (55.5%; 1.0; -) Rural (27.7%; 0.7; 0.52) WS city (33.3%; 1.0: -) Other WS (63.9%; 0.6; 0.23) HS gas (2.8%; 0.4; 0.12) HS wood (30.6%; 0.8; 0.65) HS oil (19.4%; 0.8; 0.61) HS coal (61.1%; 0.9; 0.90) Grooming (7%; 1.3; 0.58) Bathing (2%; 0.5; 0.16) |
| Snyder <i>et al.</i> , 2004 [12] | USA | III | 23 | - | M (16) F (17) | ND | Never (34.8%; 1.0) | Dry (21.7%; 1.0) | - | - |

| | | | | | | | Collar (43.5%; 0.7; 0.21) Shampoo (0) Other (21.7%; -; -) | Canned (43.49%; 0.7; 0.99) Canned tuna (52.2%; 1.1; 0.99) | | |
|-------------------------------------|-------------------|-----|----|--|------------------|------------------------------|--|--|---|-----------------|
| Pavlin <i>et al.</i> , 2018 [56] | Slovenia | V | 1 | ES (1) | M (0) F (1) | Sen (1) | - | - | Periodontal disease; Tooth resorption; Dental loss (100%) | Dental plaque |
| Olmsted <i>et al.</i> , 2016 [55] | USA | III | 35 | ES (31) Ab (1) B (1) MC (1) BN (1) | M (16) F (19) | 14 | - | - | Feline chronic gingivostomatiti s (2.8%) | - |
| Hayes <i>et al.</i> , 2007 [6] | United Kingdom | III | 54 | ES (50) MC (1) P (1) Bu (1) | M (29) F (25) | 13.3 | - | - | Dental pathology (31%) | - |
| Boston <i>et al.</i> , 2018 [74] | USA | II | 7 | ES (6) BN (1) | M (4) F (3) | AdMa (1) Sen (3) G (3) | - | - | Dental loss (14.3%) | - |
| Quigley <i>et al.</i> , 1972[68] | United Kingdom | IV | 4 | - | M (2) F (2) | AdMa (1) Sen (3) | - | - | Osteosarcoma (50%) | Dental residues |

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|----------------------------------|-------|-----|-----|----------------------------|------------------|----------|--|--|--------------------------------|--|
| Moisan <i>et al.</i> , 1998 [54] | USA | V | 1 | ES (1) | M (1) | AdMa (1) | - | - | <i>Trichinella</i> spp. (100%) | - |
| Zacone <i>et al.</i> , 2021 [73] | Italy | III | 100 | Purebred (10%) ES (90%) | M (46) F (54) | ND | Collar (3%; ;0.01) Oral products (4%; ;-) Spot - on drops (59%; ;-) | Dry (32%) Canned tuna (63%) Table scraps (20%) Food with high chemical additives(80%; ;0.01) | Oral inflammation (34%) | Trivalent vaccine occasional (52%) Trivalent vaccine regular (36%) Cohabitation with other cats (63%) Rural living environment(37%; ;-;0.04) |

ES – European Shorthair; S – Siamese; P – Persian; M – Male; F – Female; MC – Main Coon; BQ – Norwegian Forest Cat; B – Bengal; Bu – Bumese; Ab – Abyssinian; AdMa – Adult Mature; Sen – Senior; G – Geriatric; HS – Heat Source; WS – Water Source; RR – Relative risk; *p* – significance level; USA – United States of America. ^c – Possibility of choosing more than one option.

Table S5. Results of quality assessment using Downs and Black score.

| Reference | Score | Reference | Score |
|-------------------------------------|-------|-------------------------------------|-------|
| Chu <i>et al.</i> , 2019[34] | 7 | Altamura <i>et al.</i> , 2018 [27] | 4 |
| Gendler <i>et al.</i> , 2010 [47] | 6 | Munday <i>et al.</i> , 2015 [17] | 3 |
| Yamashita <i>et al.</i> , 2018 [32] | 6 | Munday <i>et al.</i> , 2019 [23] | 5 |
| Altamura <i>et al.</i> , 2020 [35] | 6 | Hoggard <i>et al.</i> , 2018 [33] | 5 |
| O'Neill <i>et al.</i> , 2011 [24] | 5 | Anis <i>et al.</i> , 2010 [36] | 4 |
| Munday <i>et al.</i> , 2009 [29] | 4 | Hutson <i>et al.</i> , 1991 [72] | 4 |
| Munday <i>et al.</i> , 2011 [30] | 5 | Supsavhad <i>et al.</i> , 2016 [31] | 3 |
| Olmsted <i>et al.</i> , 2016 [55] | 8 | Renzi <i>et al.</i> , 2019 [13] | 6 |
| Altamura <i>et al.</i> , 2016 [26] | 5 | Pavlin <i>et al.</i> , 2018 [56] | 5 |
| Bertone <i>et al.</i> , 2003 [14] | 6 | Hayes <i>et al.</i> , 2007 [6] | 6 |
| Snyder <i>et al.</i> , 2004 [12] | 5 | Boston <i>et al.</i> , 2018 [74] | 6 |
| Quigley <i>et al.</i> , 1972 [68] | 4 | Altamura <i>et al.</i> , 2020[35] | 7 |
| Moisan <i>et al.</i> , 1998 [54] | 4 | Zaccone <i>et al.</i> , 2021 [73] | 6 |