Smoking, Radiotherapy, Diabetes and Osteoporosis as Risk Factors for Dental Implant Failure: A Meta-Analysis

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Abstract

Background: There are conflicting reports as to the association between smoking, radiotherapy, diabetes and osteoporosis and the risk of dental implant failure. We undertook a meta-analysis to evaluate the association between smoking, radiotherapy, diabetes and osteoporosis and the risk of dental implant failure.

Methods: A comprehensive research on MEDLINE and EMBASE, up to January 2013, was conducted to identify potential studies. References of relevant studies were also searched. Screening, data extraction and quality assessment were conducted independently and in duplicate. A random-effects meta-analysis was used to pool estimates of relative risks (RRs) with 95% confidence intervals (CIs).

Results: A total of 51 studies were identified in this meta-analysis, with more than 40,000 dental implants placed under risk-threatening conditions. The pooled RRs showed a direct association between smoking (n = 33; RR = 1.92; 95% CI, 1.67–2.21) and radiotherapy (n = 16; RR = 2.28; 95% CI, 1.49–3.51) and the risk of dental implant failure, whereas no inverse impact of diabetes (n = 5; RR = 0.90; 95% CI, 0.62–1.32) on the risk of dental implant failure was found. The influence of osteoporosis on the risk of dental implant failure was direct but not significant (n = 4; RR = 1.09; 95% CI, 0.79–1.52). The subgroup analysis indicated no influence of study design, geographical location, length of follow-up, sample size, or mean age of recruited patients.

Conclusions: Smoking and radiotherapy were associated with an increased risk of dental implant failure. The relationship between diabetes and osteoporosis and the risk of implant failure warrant further study.

Introduction

Dental osseointegrated implants are generally considered as effective and predictable restorations for the replacement of missing teeth. However, although highly desirable outcomes and the long-term survival of dental implant treatments are well documented in numerous studies [1–4], implant failures still occur for various reasons. Therefore, the risks associated with dental implant failure have become a frequently discussed topic in recent dental research.

A variety of conditions, including implant design (length, shape or surface texture), patient-related medical risk factors (systemic diseases or habits, such as smoking), and surgery-related factors (surgeon’s experience or surgical design) have been considered to influence the outcome for implant restoration [5–7]. With the dramatic advancements in materials science and surgical techniques, increasing attention is focused on patient-related conditions as risk factors for dental implant failure [8].

According to research by Buser and colleagues, patients exposed to with irradiation (radiotherapy) before or after implantation, or patients with severe diabetes or heavy smoking habits have significantly increased risks of dental implant failure [9]. It has been suggested that such conditions could impair implant survivability by increasing the susceptibility of the patient to other diseases or by interfering with the tissue healing process [1]. Moreover, osteoporosis, with its high prevalence in the aged population, is also considered a relative contraindication for dental implant therapy [10,11]; the alveolar ridge atrophy and low bone mineral density, caused by osteoporosis may impair bone quality and quantity at implant sites [12,13]. While a number of studies have assessed the influence of smoking, radiotherapy, diabetes and osteoporosis on implant failure, the results have been inconsistent.

Since life expectancy is expected to increase with the advent of better therapies and targeted medicine, an increasing number of patients who smoke or previously smoked, who received radiotherapy for head and neck cancer treatment, or who present with diabetes or osteoporosis may require dental implant treatment.
The aim of the present study was, therefore, to provide a comprehensive and critical meta-analysis of clinical studies published in international peer-reviewed literature concerning these four factors of high prevalence and/or of high risks, in order to draw evidence-based conclusions as to the influence of these factors on the outcome of dental implant treatment.

Methods

Search Strategy

We performed a systematic literature search of MEDLINE and EMBASE database up to January 2013. All searches were performed using medical subject heading (MeSH) or free text words. We combined search terms for outcomes (survival, success, osseointegration, failure, removal, replacement and loss), risk factors (1, smoking, smoker or tobacco; 2, irradiation, radiotherapy or head and neck cancer; 3, diabetes, diabetic, diabetes mellitus or hyperglycemia; 4, osteoporosis, osteopenia, low bone mineral density or bone loss) and key subjects (dental implant or oral implant). Reference lists of identified articles and relevant papers known to reviewers were also searched. Emails were sent to the authors of identified studies for additional information, where necessary. Studies were limited to English publications. Considering the study by Mish and his colleagues, we referred implant failure.

Table 1. Criteria of Quality Assessment (a Modified McHarm checklist).

| ITEMS                                                                 | YES | NO/Not sure |
|-----------------------------------------------------------------------|-----|-------------|
| 1. Were the harms PRE-DEFINED using standardized or precise definitions? (In present study, we defined “harms” as the totality of adverse consequences of an implant surgery) | 1   | 0           |
| 2. Were SERIOUS events precisely defined? (In present study, we defined complications that didn't lead to IMPLANT LOSS or IMPLANT REMOVAL as SERIOUS events, e.g. sensitivity on function, radiographic bone loss ≤4 mm or 1/2 of the implant body, probing depth ≥7 mm, etc.) | 1   | 0           |
| 3. Were SEVER events precisely defined? (In present study, we defined IMPLANT LOSS as SERIOUS events) | 1   | 0           |
| 4. Did the study specify the TRAINING or BACKGROUND of who ascertained the harms? | 1   | 0           |
| 5. Did the study specify the TIMING and FREQUENCY of collection of the harms? | 1   | 0           |
| 6. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection? | 1   | 0           |
| 7. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group? | 1   | 0           |
| 8. Did the TOTAL NUMBER of participants affected by harms specified for each study arm? | 1   | 0           |
| 9. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group? | 1   | 0           |
| 10. Did the author(s) specify the type of analyses undertaken for harms data? | 1   | 0           |
| A Total of 10 Points                                                   |     |             |

The methodological quality of the included studies was independently and appraised twice by two reviewers (H Chen and X Xu) using elements of McMaster Quality Assessment Scale of Harms (McHarm) [13]. The criteria of the quality assessment are presented in Table 1. Any discrepancy that occurred during data extraction and quality assessment was resolved by consensus discussion with another reviewer (X Qu).

Data Extraction and Quality Assessment

Two reviewers (H Chen and N Liu) independently extracted data using a structured form. The following information was extracted from each included study: year of publication, country, first author’s family name, study design, follow-up period, characteristics of subjects (number of patients, gender and age), characteristics of implant (number and placement position) and data on dental implant failure.

Statistical Analysis

We evaluated dental implant failure for any reason attributable to the implant as our outcome measure of interest. Relative risk (RR) was used as the common measure of association across
studies. The RRs and 95% confidence intervals (CIs) were extracted or calculated from each study, and then we pooled the overall RRs using the inverse of corresponding variances as weights. For the meta-analysis, a random-effects model was considered [16]. Heterogeneity between studies was tested through the Cochran Q and I² statistics (I² values of 25, 50, and 75% are considered as low, moderate, and high, respectively [17]). Subgroup analyses were used to identify associations between the risk of dental implant failure and other relevant study characteristics (mean age, geographical location, design of study, sample size and length of follow-up) as possible sources of heterogeneity. Publication bias was measured using Begg’s and Egger’s regression tests and visualization of funnel plots [18]. The stability of the study was also detected by sensitivity analysis, through re-meta-analysis with one involved study excluded each time. All statistical analyses were performed with Review Manager 5.01 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 11 (StataCorp, College Station, TX).

Results

Literature Search
The literature search yielded a total of 3,735 primary studies, of which 3,472 were excluded after title screening. An additional 65 studies were included after checking the references of relevant reviews and studies. Finally, 328 studies were included for full-text assessment, of which 277 were excluded for one of the following reasons: (1) studies focusing on irrelevant outcome assessment (n = 144), such as bone loss or primary stability; (2) studies without a non-risk group (n = 56); (3) studies only providing patient-related data (n = 21); (4) studies where data related to implant failure could not be calculated (n = 53); and (5) studies where the reported data were represented in another included in our analysis (n = 3) [19–21]. As a result, 51 studies met the inclusion criteria for meta-analysis, with 33 studies for smoking [22–54], 16 for radiotherapy [31,44,55–68], five for diabetes [31,44,47,48,69] and four for osteoporosis [44,70–72], respectively. Of note, four studies involved more than one risk factor and were included in more than one group [31,44,47,48]. A flow diagram of the study selection process is presented in Figure 1.

Study Characteristics and Quality Assessment
The detailed characteristics of the included studies and the results of the quality assessment are summarized in Tables 2–5. The number of implants in each study ranged from 56 [34] to 5,843 [49]. The earliest study was published in 1993 [22], and the latest in 2012 [53,54,67–69]. In terms of study design, 23 studies enrolled patients prospectively [24,25,27–30,32–34,37–40,42,46,47,53,56,60–64,66,67,70–72] and 28 were retrospective database reviews [22,23,26,30,31,35,36,41,43–45,48–54,56,57,59,63,65,67,68,70–72]. By geographic location, 18 studies were conducted in the United States [24,26,30–33,35,36,40,42,44,46,50,53,57,65,71], 24 in Europe [23,27,28,29,37,43,44,49,51,52,54–56,58–64,66–68,72] and nine in other regions [22,23,34,41,46–48,69,70]. The overall study quality averaged 8.2 (range, 5–10) on a scale of 1 to 10.

Smoking
The multivariable-adjusted RRs in each study and the pooled RRs of dental implant failure for smoking versus non-smoking patients are presented in Figure 2, Table 2 and Table 6 (33 studies; 35,118 implants). In the pooled analysis, smoking was associated with higher risk of dental implant failure (RR = 1.92; 95% CI, 1.67–2.21). There was moderate heterogeneity among the studies (P = 0.03, I² = 35%). Stratifying by study design, the pooled RRs for prospective studies and retrospective studies were 1.34 (95% CI, 0.90–2.00) and 2.01 (95% CI, 1.75–2.30). Stratifying by geographical location, the summary RRs were 1.59 (95% CI, 1.27–1.98) for studies conducted in the United States, 2.27 (95% CI, 1.62–3.20) for Europe and 2.23 (95% CI, 1.77–2.81) for other regions. With regard to the mean age of patients, the pooled RRs for <55-year-old and ≥55-year-old patients were 2.15 (95% CI, 1.87–2.47) and 1.67 (95% CI, 1.13–2.47), respectively. A subgroup...
Radiotherapy

Figure 3 shows the association between radiotherapy and risk of dental implant failure from a collection of 16 studies and 5,246 implants. A pooled analysis indicated a direct association between radiotherapy and the risk of dental implant failure (RR = 2.28; 95% CI, 1.49–3.51). The heterogeneity among the studies was high (P < 0.0001, I² = 70%). As far as geographical location was concerned, the summary RRs were 1.46 (95% CI, 0.12–17.3) for studies performed in the United States and 2.29 (95% CI, 1.45–3.63) for Europe. Stratifying by length of follow-up, the pooled RRs for <5-year and ≥5-year duration were 1.76 (95% CI, 1.20–2.59) and 1.62 (95% CI, 0.85–3.11), respectively. According to the mean age of the patients involved, the pooled RRs for <55-year-old and ≥55-year-old patients were 1.95 (95% CI, 1.11–3.42) and 1.40 (95% CI, 0.33–5.97). In the subgroup analysis, study design, geographical location, length of follow-up, sample size and mean patient age, had no influence on the risk of dental implant failure (Table 6).

### Table 2. Study Characteristics (SMOKING).

| Author (Year) | Country | Study | Follow-up | Patient Characteristics | Smoking | Implant Characteristics | QS |
|---------------|---------|-------|-----------|-------------------------|---------|-------------------------|----|
| Bain, 1993    | Canada  | Retro | 37.88 m   | 54.7 yr                 | NA/NA   | 311 NA                  | 1,804/390  |
| De Bruyn, 1994| Belgium | Retro | NA (20–80 yr) | 91/26       | 66    | NA                      | 338/114  |
| Gorman, 1994  | USA     | Prospec | NA       | 228/82 NA              | NA      | 142/646 NA              | 47/2/7   |
| Bain, 1996    | Canada  | Prospec | NA       | NA/NA NA/NA            | NA      | 176/47 NA               | 9/10    |
| Minsk, 1996   | USA     | Retro | 6 yr      | 1NA/NA NA/NA/NA        | NA      | 20 per day              | 570/157  |
| Lindquist, 1997| Sweden  | Prospec | 10 yr    | (33–64 yr) 24/21       | NA      | 139/125 Mandible        | 3/0     |
| De Bruyn, 1999| Belgium | Prospec | 7 yrs    | 13/10 NA               | 13.2 per day | 13/202 NA          | 9/6/10  |
| Grunder, 1999 | Switzerland | Prospec | 34.4 m 58±15 yr 55/19 | 34 NA | 164/55 NA               | 3/0/9   |
| Jones, 1999   | USA     | Retro | 58 m 50 yr | 44/19        | 40 NA | 217/126 204/17        | 5/11/8   |
| Keller, 1999  | USA     | Retro | 12 yr (15–73 yr) | 26/28 NA   | NA | 143/105 Grafted maxilla sinus | 26/7/10 |
| Lambert, 2000 | USA     | Prospec | 3 yr NA | NA/NA NA               | NA      | 1,928/959 1616/1271    | 115/85   |
| Olson, 2000   | USA     | Prospec | 38±15 m 56±12 yr | 1 NA | 65/51 Grafted maxillary sinus | 1/2     |
| Wallace, 2000 | USA     | Retro | 4 yr     | 39/17 NA               | NA      | 115/72 NA              | 8/12    |
| Schwartz-Ara, 1999 | Israel | Prospec | 5 yr 47 yr | NA/NA NA               | 27 NA | 50/6 39/17           | 5/1/7    |
| Geurs, 2001   | USA     | Retro | 3.2±1.3 yr | 13/17 NA | 164/55 Maxilla sinus | 3/7/6 |
| Widmark, 20001| Sweden  | Prospec | 3–5 yr 25/11 NA | 21/11 NA | 131/67 Local: 120/Grafted: 101 | 14/26    |
| Kumar, 2002   | USA     | Prospec | NA       | 389/72 NA              | NA      | 914/269 357/826 NA    | 8/15/5   |
| Van Steenberghe, 2002 | Belgium | Prospec | NA       | 50±14 yr NA/NA NA    | 243 NA | 1,107/156 NA         | 19/8     |
| Karoussis, 2003 | Switzerland | Prospec | 10 yr 41/12 NA | NA      | 84/28 NA              | 3/2/10  |
| DeLuca, 2006  | Canada  | Retro | 59.8 m 49.3 yr | 285/104 283| NA | 1,045/4,94 NA        | 32/26/9  |
| Peleg, 2006   | USA     | Prospec | 69 m NA | 505/226 453 NA | NA | 1,505/627 Maxilla sinus grafting | 28/16/7  |
| Mundt, 2006   | Germany | Retro | 88.2 m 54.1 yr | NA/NA NA | 249/363 246/367 | 6/30/8   |
| Alsaaedi, 2008 | Belgium | Retro | 2 yr NA | 351/61 240 NA | NA | 1,291/223 698/816 | 80/21/8  |
| Balshe, 2008  | USA     | Retro | 5 yr 49.4 yr | 1699/119 | 861 17.7±7 per day | 3,841/766 2,633/1974 | 188/77/7  |
| Levin, 2008   | USA     | Prospec | 6.14 yr 45 yr | 54/10 40 NA | 54/10 NA | 3/1/7    |
| Tawill, 2008  | Lebanon | Prospec | 42.4 m NA | 50/40 33 NA | 254/245 NA | 2/5/9 |
| Anner, 2010   | Israel  | Retro | 31±28 m 52±12 yrs | 412/63 299 | NA | 1,400/226 NA      | 56/21/7  |
| Cavalcanti, 2011 | Italy  | Retro | 5 yr 50 yrs | 1019/458 1025 | NA | 3,882/1,961 NA | 112/107/9 |
| Conrad, 2011  | USA     | Retro | 35.7 m 55.3 yr | NA/NA NA | 446/48 Maxilla | 28/6/8  |
| Rodriguez, 2011 | Spain  | Retro 6 m | 53±13 yr 182/113 188 NA | 664/389 NA | 18/14/9|
| Vandeweghe, 2011 | Belgium | Retro | 22 m 54±13.4 yr | 288/41 43 NA | 608/104 NA | 7/5/9 |
| Lin, 2012     | USA     | Retro | 12 m 59.6 yr | 47/28 186 NA | 93/62 Grafted maxilla sinus | 12/13/9 |
| Vervaeke, 2012 | Belgium | Retro | 31±7.2 m 56±12 yr | 235/60 168 NA | 244/849 458/648 | 11/8/10 |

CON = control group, that is non-smoking group; STY = study group, that is smoking group; F = Female; Mand. = mandible; Max. = maxilla; Retro = retrospective study; Prospec = prospective study; yr = year; m = month; NA = not available; Local = local bone; Grafted = grafted bone; FC = failure implant number of Control Group; FS = failure implant number of Study Group; QS = quality assessment score.

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Diabetes and Osteoporosis

Five studies were included to analyze on dental implant failure with regard to diabetes (6,774 implants). The results of the pooled analysis are shown in Figure 4. The pooled RR for patients with diabetes versus patients without diabetes was 0.90 (95% CI, 0.62–1.32), indicating no association between diabetes and the risk of dental implant failure. We found high heterogeneity across the studies ($P=0.07$, $I^2=58\%$).

Four studies were concerned with the association between osteoporosis and dental implant failure, with a collection of 3,070 implants. In the pooled analysis, the association between osteoporosis and the risk of dental implant failure was direct but not significant ($RR=1.09; \text{ 95\% CI, 0.79–1.52}$), with high heterogeneity across the studies ($P=0.14$, $I^2=46\%$). (Figure 5)

Since limited studies focusing on diabetes and osteoporosis met our inclusion criteria, and insufficient data could be extracted from the included studies, no subgroup analysis was performed to further investigate the association between diabetes and osteoporosis and risk of dental implant failure.

Publication Bias and Sensitivity Analysis

Publication bias was determined by visualization of funnel plot, Begg’s test, and Egger’s regression test. With the exception of radiotherapy (Begg’s test: $P=0.47$; Egger’s test: $P=0.02$), there was no evidence of publication bias for smoking (Begg’s test: $P=0.47$; Egger’s test: $P=0.02$).

**Table 3. Study Characteristics (RADIOThERAPY).**

| Author (Year) | Country | Study  | Follow-up | Patient Characteristics | Radiotherapy | Implant Characteristics | QS |
|---------------|---------|--------|-----------|------------------------|-------------|-------------------------|----|
| Esser, 1997   | Germany | Prospec| NA        |                          |             |                         | 73 |
| Werkmeister, 1999 | Germany | Retro  | 3 yrs     | (37–79 yr)              | NA/NA       | 9 BP 60 66/152          |    |
| Keller, 1999  | USA     | Retro  | 12 yrs    | (15–73 yr)              | NA/NA       | 55 and 61 237/11        | 33/0|
| Shaw, 2005    | UK      | Retro  | 3.5 yr    | 58 yr                   | 43/34       | BP 40–66                |    |
| Yerit, 2006   | Austria | Prospec| 5.4±3.2 yr| 58±14 yr                | NA/NA       | BP 50                   | 15/29|
| Schepers, 2006 | Netherlands | Retro | up to 23 m| 66.11 yr                | 27/21       | AP 60–68 78/61          | 0/2 |
| Landes, 2006  | Germany | Prospec| 36 m      | 63 yr                   | 11/19       | BP 57                   |    |
| Nelson, 2007  | Germany | Prospec| 10.3 yr   | 59 yr                   | NA/29       | BP up to 72 311/124     | 4/7 |
| Alsaadi, 2008 | Belgium | Retro  | 2 yr      | NA                      | 410/2       | BP 1499/15 698/816      | 98/3|
| Schoen, 2008  | Netherlands | Prospec | 12 m  | 62±11 yr                | 16/19       | AP 60.1±7.7 64/76       | 2/9 |
| Klein, 2009   | Germany | Prospec| 5 yr      | 58.4 yr                 | 16/27       | BP <50 or ≥50 74/116     | 12/38|
| Cuesta-Gil, 2009 | Spain | Prospec | /        | 52 yr                   | 32/79       | Mixed 50–60 311/395     | 6/75|
| Salinas, 2010 | USA     | Retro  | 41.1      | NA                      | 18/26       | Mixed >60 116/90        | 8/23|
| Linsen, 2012  | Germany | Prospec| 48.3±3.4 m| 56±16 yr                | 32/34       | BP 36 or 60 135/127     | 6/8 |
| Jacobsen, 2012 | Switzerland | Prospec | 67 m | 52.4 yr                | NA/NA       | AP 93/47                 | 14/14|
| Fenlon, 2012  | UK      | Retro  | /         | NA                      | 29/12       | NA 110/35                | 3/15|

CON = control group, that is non-radiotherapy group; STY = study group, that is radiotherapy group; F = Female; BP = before placement; AP = after placement; Mand. = mandible; Max. = maxilla; Retro = retrospective study; Prospec = prospective study; yr = year; m = month; NA = not available; Local = local bone; Grafted = grafted bone; FC = failure implant number of Control Group; FS = failure implant number of Study Group; QS = quality assessment score.

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**Table 4. Study Characteristics (DIABETES).**

| Author (Year) | Country | Study  | Follow-up | Patient Characteristics | Diabetes Type | Implant Characteristics | QS |
|---------------|---------|--------|-----------|------------------------|---------------|-------------------------|----|
| Keller, 1999  | USA     | Prospec| 12 yrs    | (15–73 yr)             | NA/NA         | 237/11 Grafted maxilla  | 0/0 |
| Morris, 2000  | New Zealand | Prospec | 36 m | NA                      | 408/255       | Mixed 180/20            | 7   |
| Tawil, 2008   | Lebanon | Retro  | 42.4 m    | 62.15 yr               | NA/NA         | II 244/255 Mixed        | 2/7 |
| Alsaadi, 2008 | Belgium | Retro  | 2 yr      | NA                      | 402/10       | II:1 59 698/816         | 202/0|
| Anner, 2010   | Israel  | Prospec| 31±28 m   | 52±12 yr               | 426/49       | 299 1,449/177 Mixed     | 72/5|

CON = control group, that is non-diabetes group; STY = study group, that is diabetes group; F = Female; Mand. = mandible; Max. = maxilla; Retro = retrospective study; Prospec = prospective study; yr = year; m = month; NA = not available; Local = local bone; Grafted = grafted bone; FC = failure implant number of Control Group; FS = failure implant number of Study Group; QS = quality assessment score.

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### Table 5. Study Characteristics (OSTEOPOROSIS).

| Author (Year) | Country | Study Follow-up | Patient Characteristics | Implant Characteristics | QS |
|---------------|---------|----------------|-------------------------|-------------------------|----|
| Amorim, 2007  | Brazil  | Retro 9 m      | Mean Age: 58.2 yr        | CON/STY: 20/19 F: 39    | 43/39 Mandible: 0/1 FC/FS: 8 |
| Alsaadi, 2008 | Belgium | Retro 2 yr     | Mean Age: NA             | CON/STY: 393/19 F: 240  | 1,446/68 698/816 92/9 F: 8 |
| Holahan, 2008 | USA     | Retro 5.4 yr   | Mean Age: 63±9 yr        | CON/STY: 564/192 F: 746 | 306/340 378/268 17/20 F: 7 |
| Dvorak, 2011  | Austria | Retro 6±4 yr   | Mean Age: 45 yr          | CON/STY: 115/62 F: 117  | 543/258 396/432 17/20 F: 7 |

CON = control group, that is non-osteoporosis group; STY = study group, that is osteoporosis group; F = Female; Mand. = mandible; Max. = maxilla; Retro = retrospective study; Prospec = prospective study; yr = year; m = month; NA = not available; Local = local bone; Grafted = grafted bone; FC = failure implant number of Control Group; FS = failure implant number of Study Group; QS = quality assessment score.

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**Figure 2. Forest plot of studies with dental implant failure risk for smoking versus non-smoking patients.** The combined Relative risks (RR) and 95% confidence intervals (CIs) were calculated using the random-effects model.

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Table 6. Subgroup analysis to investigate differences between studies included in meta-analysis.

| Smoking Design of Study | No. of Studies | RR (95% CI) | P (%) | P value | P value for heterogeneity between subgroups |
|-------------------------|----------------|-------------|-------|---------|------------------------------------------|
| Prospective             | 15             | 1.34(0.90,2.00) | 67    | <0.0001 | 0.06                                     |
| Retrospective           | 18             | 2.01(1.75,2.30) | 14    | 0.29    |                                          |

Geographical Location

| Length of Follow-up (years) | No. of Studies | RR (95% CI) | P (%) | P value | P value for heterogeneity between subgroups |
|-----------------------------|----------------|-------------|-------|---------|------------------------------------------|
| ≥5                          | 11             | 1.72(1.37,2.15) | 28    | 0.18    | 0.32                                     |
| <5                          | 17             | 1.98(1.68,2.33) | 14    | 0.29    |                                          |

Sample Size (implant)

| Age (years) | No. of Studies | RR (95% CI) | P (%) | P value | P value for heterogeneity between subgroups |
|-------------|----------------|-------------|-------|---------|------------------------------------------|
| <55         | 11             | 2.15(1.87,2.47) | 0     | 0.67    | 0.23                                     |
| ≥55         | 6              | 1.67(1.13,2.47) | 0     | 0.54    |                                          |

Radiotherapy Design of Study

| Radiotherapy Design of Study | No. of Studies | RR (95% CI) | P (%) | P value | P value for heterogeneity between subgroups |
|------------------------------|----------------|-------------|-------|---------|------------------------------------------|
| Prospective                  | 6              | 2.02(1.37,2.97) | 0     | 0.73    | 0.58                                     |
| Retrospective                | 10             | 2.50(1.32,4.75) | 81    | <0.00001|                                          |

Geographical Location

| Length of Follow-up (years) | No. of Studies | RR (95% CI) | P (%) | P value | P value for heterogeneity between subgroups |
|-----------------------------|----------------|-------------|-------|---------|------------------------------------------|
| ≥5                          | 5              | 1.62(0.85,3.11) | 62    | 0.03    | 0.83                                     |
| <5                          | 8              | 1.76(1.20,2.59) | 20    | 0.27    |                                          |

Sample Size (implant)

| Age (years) | No. of Studies | RR (95% CI) | P (%) | P value | P value for heterogeneity between subgroups |
|-------------|----------------|-------------|-------|---------|------------------------------------------|
| <60         | 8              | 1.95(1.11,3.42) | 78    | <0.0001 | 0.68                                     |
| ≥60         | 3              | 1.40(0.33,5.97) | 0     | 0.69    |                                          |

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Discussion

Principle Findings

After reviewing numerous studies assessing the potential risk factors for dental implant failure, this meta-analysis supports the view that smoking and radiotherapy are associated with a higher risk of dental implant failure. Our findings suggest that individuals who smoke, or who have undergone radiotherapy before or after implantation, might suffer an approximately 35 or 70% higher risk of dental implant failure, respectively, as compared with non-smokers or those who have not been exposed to radiotherapy. We found no significant inverse impact of diabetes on the risk of dental implant failure, whereas osteoporosis showed a direct but not significant association. However, because of the limited number of studies focusing on diabetes and osteoporosis, these results should be interpreted carefully and verified by further studies. The findings of this meta-analysis, may offer clinical dentists with additional insights into the prognosis of dental implant treatment and may help in the establishment of potential treatment plans.

Implications

The outcome of this meta-analysis indicated that individuals who smoke were more likely to suffer from dental implant failure. This finding is consistent with a previous meta-analysis performed in 2006, with an elevated OR of 2.17 (95% CI, 1.67–2.83) indicating the inverse impact of smoking on implant osseointegra-
tion [73]. Although the underlying mechanism is still not completely understood, researchers previously posited that smoking impaired the wound healing processes involved with implant/tissue integration [27]. Others suggested that smokers treated with implants had an increased risk of postoperative complications, such as infection and peri-implantitis [53]. Bain and colleagues recommended that patients commence a smoking cessation protocol at least one week before and at least two months after dental implant surgery to assure dental implant osseointegration [22]; however, others have demonstrated that pre-operative smoking cessation, especially short-term cessation, bears no significant effect on reducing the risk of dental implant failure [74].

The present meta-analysis indicates that radiotherapy was strongly associated with increased risk of dental implant failure. A former review of animal and human studies reached a similar conclusion that implants placed in irradiated bone experienced 2–3 times higher rates of failure [75]. Moreover, implants placed in irradiated maxilla were reported to have a higher failure rate compared with those in irradiated mandible [76]. Bone responds to irradiation with various cellular, vascular, and metabolic alterations occurring at different sites in the irradiated bone and adjacent tissues [77]. Several plausible mechanisms to explain how bone responds to irradiation have been proposed, including altered osteoblast and osteoclast function during bone repair and remodeling, the formation and the subsequent breakdown of hypoxic-hypocellular and hypovascular tissues, and a decreased rate of tissue perfusion and tissue fibrosis [77–79]. Such responses were previously believed to be highly variable and partly related to the administered dose of radiation [77]. Researchers suggested that a fractionated dose would be better tolerated than a single exposure at the same level of intensity [80]. Furthermore, adjunctive treatment with the use of hyperbaric oxygen (HBO) was expected to increase the regenerative capacity of tissue damaged after radiotherapy; however, no strong evidence was found to support the use of HBO to decrease dental implant failure for radiotherapy-exposed patients [81].

Figure 3. Forest plot of studies with dental implant failure risk for patients with radiotherapy versus non-smoking. The combined Relative risks (RR) and 95% confidence intervals (CIs) were calculated using the random-effects model.
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Figure 4. Forest plot of studies with dental implant failure risk for patients with diabetes versus non-diabetes. The combined Relative risks (RR) and 95% confidence intervals (CIs) were calculated using the random-effects model.
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Diabetes and osteoporosis are both highly prevalent disorders among elderly patients [10,11,82]. After reviewing the published literature, we found a lack of high quality and single-risk-factor focused studies with regard to the effects of diabetes or osteoporosis on dental implant survival. The present meta-analysis revealed no direct impact of diabetes or osteoporosis on the risk of dental implant failure, although both were reported to affect wound healing in oral tissues [1]. Clinical dentists are advised to avoid dental implant treatment in poorly controlled diabetic patients, and studies indicate that the long-term use of bisphosphonates by osteoporotic patients may cause osteonecrosis of the jaw [83]. Unfortunately, data was insufficient yet to give an explicit explanation of its effect on risk of dental implant failure. Diabetes and osteoporosis can be well controlled by drug intervention; yet since, none of the studies included a discussion as to the different level of severity of diabetes or osteoporosis in these patients and on the risk of dental implant failure, this limited our ability to further assess the risk of these two factors in the present meta-analysis.

Strength and Limitations

To our knowledge, this study is the most comprehensive meta-analysis to estimate the association of smoking, radiotherapy, diabetes, and osteoporosis with dental implant failure. We were able to include a substantial total number of subjects (more than 40,000 dental implants placed under risk-threatening conditions), which significantly increased the statistical power of our analysis. We made sure to minimize the bias by means of study procedure. Not only did we search MEDLINE and EMBASE databases to identify potential studies, but also we manually examined all reference lists from relevant studies. The McHarm quality assessment tool was used to evaluate each of the included studies to ensure sufficient study quality (mean score of 8.2 out of 10). Publication bias was also absent, as determined by visualization of funnel plot, Begg’s test and Egger’s test.

Despite the above strengths and advantages, this meta-analysis has several limitations. First, the present study was subject to confounding factors that could be inherent in the included studies and it is difficult to completely rule out the possibility that other risk factors were responsible for the observed associations. Second, heterogeneity might have been introduced by methodological differences among the studies. Many of the \( I^2 \) estimates calculated in this meta-analysis were judged as high. While we were able to perform subgroup analyses on studies of smoking and radiotherapy, which indicated no influence on the study design, geographical location, length of follow-up, sample size and mean patient age, the diabetes and osteoporosis implant failure data were insufficient for a stratified analysis. Although these issues might have reduced the strength of the conclusions drawn in this meta-analysis, visual inspection of the forest plots suggests that there is considerable consistency in the RRs across the studies. Third, the search was limited to English studies and only performed with the use of two electronic databases, mainly because of the limited work force for the present research; this might have introduced a selection bias to the results.

Suggestion for Future Studies

On the basis of this meta-analysis, several questions should be answered in future studies. First, what is the compound effect of multiple risk factors on dental implant failure? For instance, what is the risk of dental implant failure for smokers with diabetes, or smokers with osteoporosis? To answer this question, several well-designed cohort studies with adequate control for confounding factors should be considered. Second, could different severity levels of the four risk factors, such as the severity of the disease or the frequency of smoking, have an effect on dental implant failure? An investigation that specifically focuses on the quantity of smoking, the overall irradiation dose, and/or the severity of diabetes and osteoporosis may offer insight into this question. Third, could the application of smoking cessation or HBO treatment as an adjunct to radiotherapy decrease the risk of dental implant failure? Future studies, including randomized controlled trials, concerning the topics are needed to gain a better understanding of the underlying relationship among these risk factors.

Conclusions

The present study investigated the influence of smoking, radiotherapy, diabetes and osteoporosis on dental implant failure, and may provide clinical dentists with additional insight for dental implant treatment prognosis and treatment strategies. We found that, smoking and radiotherapy are associated with a higher risk of dental implant failure while diabetes has no significant inverse impact on the risk of dental implant failure. The association between osteoporosis and the risk of dental implant failure was direct but not significant. However, because of the lack of high quality and individual risk-isolated studies with respect to diabetes and osteoporosis, additional, well-designed studies, with adequate control for confounding factors, are required in future investigations.

Supporting Information

Checklist S1  PRISMA Checklist. (PDF) (PDF)
Figure S1 Funnel Plot of Smoking, Radiotherapy, Diabetes and Osteoporosis. (PDF)

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Author Contributions

Conceived and designed the experiments: HC XQ EL. Performed the experiments: HC NL XX. Analyzed the data: HC NL XX XQ. Contributed reagents/materials/analysis tools: HC XQ. Wrote the paper: BX XQ EL.
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