Tooth whitening, smoking and cancer
This evidence summary aims to locate and summarise evidence on if there is an increased risk of oral cancer for tooth whitening in patients who smoke. It does not include detailed descriptions of the studies cited nor does it include information that was not presented in the literature.

The Curious about website encourages dental professionals to raise issues where a review of the available evidence would provide a useful resource for other dental professionals.

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Key findings

• There is no evidence to suggest that whitening and smoking have a synergistic effect on the risk of oral cancer
• There is inadequate evidence in humans for the carcinogenicity of hydrogen peroxide.

Review question

This evidence summary was prepared in response to the following question: Is there an increased risk for oral cancer when tooth whitening is combined with smoking?

Aim

To assess the effects of tooth whitening on the development of cancer in people who smoke. For this summary the term smoking will exclude the use of smokeless tobacco and e-cigarettes.

The case for action

Tooth whitening

Tooth colour has become an increasingly aesthetic concern in recent years with public demand for tooth whitening increasing.(1) Tooth aesthetics is important to many patients(1) and whitened teeth may influence quality of life as they improve satisfaction with dental appearance.(2) Fifty percent of a UK study sample reported stained teeth and satisfaction with tooth colour decreased with increasing perceived severity of discolouration.(3) Females were less likely to perceive having discoloured teeth than males and prevalence of discolouration appeared to increase with increasing age. Having lower than the national average income was associated with higher prevalence of perceived tooth discolouration(3) and younger adults tended to have a lesser degree of satisfaction with their dental appearance than older individuals.(4)

Types of tooth whitening

There are a number of approaches to manage tooth discoloration and peroxide-containing whiteners can be classified into three categories:(5;6)

• Those containing high concentrations of peroxides for professional use only
• Materials dispensed by dentists and used by patients at home
• Over-the-counter products, such as whitening strips, gels, toothpastes and dentifrices, available directly to consumers for home use.

Compared with restorative or prosthetic treatments for discolouration whitening is the most conservative approach.(1) Whitening agents can be applied externally to teeth (vital bleaching) or within the pulp chamber (non-vital bleaching).(7)

How tooth whitening works

Tooth whitening products have been in use for over 100 years.(8) Current methods usually involve oxidation with a whitening agent entering the enamel/dentine of the affected tooth.(8) Contemporary commercial whitening products are based primarily on hydrogen peroxide (H₂O₂), an oxidising agent, or a pre-cursor such as carbamide peroxide, used in combination with an activating agent for example heat and/or light.(7) H₂O₂ diffuses through the tooth enamel and dentine and dissociates to produce free radicals.(8;9) These radicals attempt to become more stable by attacking organic molecules in the spaces between the inorganic salts in tooth enamel resulting in the creation of smaller more simple molecules that reflect less light and creating a whitening action.

H₂O₂ can damage oral soft and hard tissues if used inappropriately.(7) Ultimately whitening results in the breakdown and loss of tooth enamel so it is crucial for dentists to know when to stop the process. Excess oxidation would lead to tooth brittleness and increased porosity.(8) A major adverse effect of tooth whitening is tooth hypersensitivity (usually transient)(10) and soft tissue irritation during or immediately following whitening.(11)

Why tooth whitening might contribute to cancer

Due to being used widely in dental products, including tooth-whitening systems, H₂O₂ has become the subject of discussion as concerns have been raised about its safety as a tooth whitening agent in relation to possible carcinogenicity.(11) H₂O₂ is mostly used during industrial processes such as the production of chemicals, textile and paper manufacturing and water and sewage treatment processes.(12;13)
The International Agency for Research on Cancer (IARC) evaluated the evidence of the carcinogenic risk of H₂O₂ in 1999 as part of their programme to evaluate the carcinogenic risk of chemicals to humans and concluded that there was inadequate evidence that H₂O₂ is carcinogenic in humans and only limited evidence in experimental animals. As a result, it was not classifiable as to its carcinogenicity to humans.  

The IARC found one case controlled human study where about 0.7% of the subjects had been exposed to H₂O₂. The study estimated the associations between workplace substances including H₂O₂ and several types of cancer and found no indication of an excess risk of cancer due to H₂O₂ exposure. Mice, hamsters and trout have been exposed to H₂O₂ orally, by skin application and subcutaneously, to determine its carcinogenicity in animals. Adenomas and carcinomas of the duodenum were reported following oral administration. Other animal studies were identified but proved inadequate for an evaluation of carcinogenicity.

Data relevant to the potential carcinogenic mechanisms of H₂O₂ was evaluated. H₂O₂ is genotoxic and has induced DNA damage in prokaryotic and eukaryotic cell systems. DNA damage included sister chromatid exchanges, chromosomal aberrations, single-strand breaks and fragmentations. Unscheduled DNA synthesis, gene overexpression and transformations were also noted.

A more recent review (2000) concluded that, based on the results of in vivo genotoxicity assays and long-term biosays, tumour production will not occur in humans as a result of exposure to H₂O₂ particularly from oral care products for daily use. The authors believed there was no likely hazard associated with the long-term use of H₂O₂ at concentrations found in oral care products.

In vitro testing has been invaluable in understanding the mechanisms of action of H₂O₂ and allowed classification of its mutagenic and genotoxic actions and its potential involvement in carcinogenesis. One reason why this work is not sufficient to study the potential carcinogenic effect of whitening products is that in vitro systems lack many of the protective mechanisms present in intact mammalian systems. 

Since the publication of the IARC evaluation and the Desesso review a number of clinical studies looking at the effects of whitening agents on the oral mucosa have been published. Two looked at possible genotoxic effects. Hydrogen peroxide and carbamide peroxide were examined. The first study concluded that whitening preparations caused damage to the genome of oral mucosal cells but that it was not possible to estimate their genotoxic potential and the second study concluded that 10% carbamide peroxide was a potential irritant of the oral epithelium and may accelerate non-detected in situ carcinomas. The authors of both studies suggested a cautious interpretation should be made of their work highlighting that they are exploratory studies producing results that should be tested and verified with additional work. Additionally the study populations were not large (n = 22 and 11 respectively) and biological processes such as proliferation do not necessarily mean that the agent has genotoxic potential.

Some suspicious cases of early-onset oral cancer have been investigated adding to the suggestion that tooth whiteners may have a role to play in oral cancer. The work is reported to involve 19 patients with head and neck cancer with three patients using tooth whiteners. All three patients with a history of whitener use presented with node-positive disease as opposed to three of 16 patients (19%) without such a history. The authors state that the data suggests that patients who use tooth whiteners were more likely to present with metastatic lymph nodes but stress that the data do not necessarily suggest a causative relationship between the use of peroxide products and the development of oral cancer. The limitations of the study, due to the small number of participants, is also noted.

Smoking

Nearly a fifth (18.3% - approximately 11.8m people) of adults living in the UK are cigarette smokers. Cigarette smoking is more prevalent in men (20.7%) than women (15.9%) with adults in routine and manual occupations more than twice as likely to be cigarette smokers than adults in managerial and professional occupations. While cigarette smoking is declining, and has been since 2010, it is still the single most important driver of health inequalities. The more disadvantaged someone is, the more likely they are to smoke and to suffer from smoking-related disease and premature death.

Cancer

There were 296,863 new cancer registrations and 147,000 cancer deaths in England in 2014. The most common cancers in England are breast, prostate, lung and colorectal cancer with 50.2% of total registrations in those aged 70 and above. There is some geographical variation with incidence being higher in the North than the South. Overall cancer incidence has increased while related deaths has decreased.

The financial burden of cancer in the UK is £15.8bn a year, £2.4bn of which relates to lung cancer (more than any other cancer). Half of the total economic cost of cancer to the UK is due to premature deaths and time off work, followed by healthcare costs (£5.6bn) and unpaid care to cancer patients by friends and family (£2.6bn).
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Smoking and cancer
Smoking has long been recognised as hazardous to health; the hypothesis that tobacco is linked to lung cancer was made in 1912. From the 1920s work repeatedly confirmed an association between lung cancer and tobacco smoking. Concerns often focused on its impact on the social and moral fabric of society; the medical community commented little on the decision to smoke or not. Warnings to the public were limited to the misleading medical claims increasingly seen in advertising and not the effects on health.

These early studies provided the evidence on smoking and lung cancer for the 1964 report of the Surgeon General written in response to the accumulating evidence in this area. This report, regarded as one of the seminal public health achievements our time, stated that cigarette smoking was a cause of lung, lip and laryngeal cancer in men. An association between smoking and bladder and oesophageal cancer was suggested but the evidence did not support a causal relationship. The relationship between smoking and other forms of oral cancer could not be stated.

The 2004 Surgeon General’s Report concluded that smoking affects nearly every organ of the body and linked to cancers of the oropharynx, larynx, oesophagus, trachea, bronchus, lung, stomach, pancreas, kidney, urethra, cervix, oral cavity and bladder as well acute myeloid leukaemia. The risk of cancer is significantly elevated in smokers who abuse alcohol with a reported synergistic effect of these two factors.

Tobacco use is one of the main risk factors for cancer in the oral cavity and since hydrogen peroxide can act as a promoter, it is possible that there is an increased risk of oral cancer in those with an elevated risk due to tobacco use.

The evidence
There has been no clinical trial publications covering cancer deaths, registrations or incidence in relation to tooth whitening and smoking. One trial histologically evaluated the genotoxicity and efficacy of at home whitening in smokers and non-smokers. This single-blind controlled study concluded that at-home whitening did not induce DNA damage to the gingival tissue during the whitening period.

The study compared 30 smokers and non-smokers using 10% carbamide peroxide for three hours a day for three weeks. Exfoliated oral mucosa was collected before and immediately after the third week of at-home whitening. The collected cells were examined for the presence of micronuclei (MN) as an indirect marker for genome damage. The whitening procedure did not increase the frequency of MN though the frequency of MN was significantly higher in smokers than non-smokers regardless of the whitening procedure.

Discussion
There is no evidence to suggest that the use of tooth whitening products together with smoking put users at a greater risk of oral cancer. There was a dearth of literature involving smokers with only one study being found. Smoking was noticed as a common exclusion factor in studies investigating tooth whitening and this may explain why only one publication was located. Since the IARC published its evaluation of H2O2 in 1999, studies have further evaluated its carcinogenic abilities with some evidence that it is genotoxic. Also, exploratory studies have involved human subjects with most looking at the effects of whitening agents but not carcinogenic outcomes. The suggestion has been made that as oral mucosal cells have a short lifespan it is probable that mild exposure to genotoxic processes, as tooth whitening represents, has negligible carcinogenic potential.
Methods

Search strategy

Controlled vocabulary (CV) terms and free text were used for searching with the search string consisting of three sections: terms and text covering tooth whitening, oral cancer and smoking. CV terms included:

- head and neck neoplasms
- Tooth Whitening
- Dentifrices
- Toothpaste
- Tooth whitening agents
- Hydrogen Peroxide
- peroxides
- Urea
- smoking
- Tobacco products
- Tobacco use

No language limits were used but search terms were only in English with results limited to years 1997 - 2017. Grey literature was searched and a snowballing strategy was employed once publications relating to the questions were located as well as to supplementary data searches using terms covering DNA damage. Ovid and Cochrane searches were repeated in January 2017 and nothing relevant was located.

Papers were included if they met the following criteria:

- Clinical trails or epidemiological studies
- Reported outcomes were:
  - Cancer registrations
  - Cancer deaths
  - Cancer incidence
  - Cell proliferation.

Papers were excluded if:

- They reported in vivo animal studies
- Were in vitro tests
- They did not compare smokers and non-smokers
- Studies had no fixed outcome.

Databases searched were:

- Medline (OVID and PubMed)
- Cochrane
- EMBASE
- Cochrane CENTRAL
- DOAJ
- BBO
- IndMed
- German National Library of Medicine (DBIS) (LIVIVO)
- OpenSIGLE
- Opengrey
- WHO ICTRP
- The UK Clinical Trials Gateway

Results

One publication was located that investigated any association between cancer, tooth whitening and smoking.(16)

References

Tooth whitening, smoking and cancer


## Appendix one

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Population</th>
<th>Aim</th>
<th>Outcomes (relevant)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Geus 2015 [16]</td>
<td>Controlled single-blind nonrandomized clinical trial</td>
<td>60 adults (aged 18 – 40 years) southern Brazil</td>
<td>Evaluate the efficacy and genotoxicity of at-home whitening in smokers and non-smokers</td>
<td>Micronuclei (MN) frequency.</td>
<td>At-home whitening did not induce DNA damage to the gingival tissue during the whitening period.</td>
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Appendix One: Study included in this summary.