Oesophageal Cancer in the Islamic Republic of Iran: Country Health Profile and Systematic Review

ABSTRACT

Background Iran has made much progress toward improving its country's healthcare over recent decades, and it is relatively advanced in epidemiological transition for its region. **Introduction** One consistent abnormality in its health profile which is not yet fully understood is Iran's high rates of oesophageal cancer (OC), which is primarily focussed in north-eastern provinces. **Methods** This systematic literature review aimed to review the most recent literature on possible associations with OC and thus aetiology and determinants for the rates observed, by means of a literature database search. **Results and Discussion** Eight papers which fitted the inclusion criteria as detailed in the methods were reviewed. The strongest evidence was seen for associations between OC and social and economic status, oral health and hot tea drinking. Weaker evidence was seen for familial history, opium and tobacco usage and H. pylori infection. **Conclusions** The reviewed evidence is useful in suggesting associations and possible aetiology of OC. However, further research, possibly in the form of cohort studies, is necessary to ensure interventions are planned and implemented effectively. These could potentially include public health programmes to improve oral health and more general governmental programmes to improve social and economic status.

BACKGROUND

Iran is a diverse country which has made significant progress in improving the population's health over the last few decades. Under-five child mortality has been more than halved from 65 deaths per 1000 children, to 26 per 1000 children in the past 15 years(1). Although 31% of the population live in rural areas, vaccine uptake is excellent: 99% of 1-year-olds were immunized against Measles and Polio in 2009(1). Iran has also more than tripled its per capita total expenditure on health since 1995 from 199 PPP$ to 685 PPP$ in 2009(1). Iran is relatively advanced in terms of epidemiological transition for its region, as shown by the data in figure 1. Consequently, rates of non-communicable disease in Iran are relatively high. As such, ischaemic heart disease, cerebrovascular disease and hypertensive heart disease all feature highly on Iran's most common

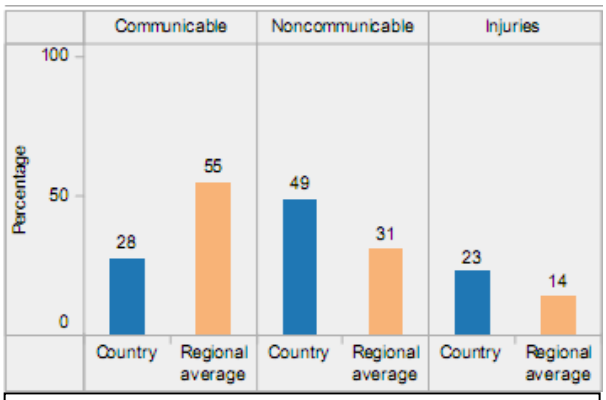


Figure 1: Distribution of years of life lost by causes in Iran (2008). Source: WHO {{20 World Health Organisation}}.

causes of death(2). Iran's health profile does have some particular peculiarities; notably the UN Office on Drugs and Crime estimated Iran to have the highest consumption of opium in the world, at 452 tons in 2008(3). The country undoubtedly owes this rate of usage (42% of the world's consumption – see figure 2) at least in part to availability, considering Iran is adjacent to the world's biggest cultivator of poppies, Afghanistan. Whilst this will certainly have health consequences, the focus of this paper is another (but potentially related) peculiarity in Iranian epidemiology – oesophageal cancer rates.

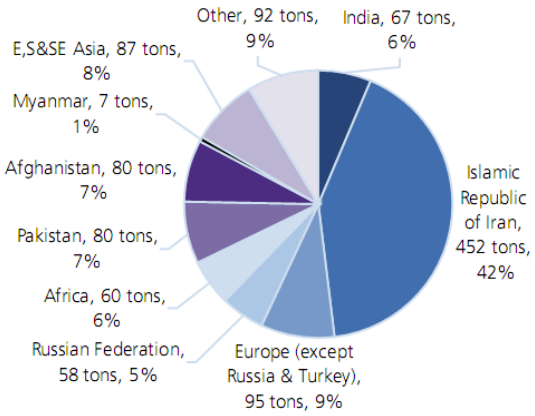


Figure 2: Estimated global opium consumption in 2008. Source: UNODC{{22 UNODC 2010}}

INTRODUCTION

Several papers over the past forty years have reported and commented on the striking rates of oesophageal cancer (OC) in Iran(4-6). Many studies focus on particular regions of Iran, generally in the north and north east, as these areas tend to have a much higher incidence of OC than other regions, which are much more comparable to the global average. For instance, the rate of OC was reported to be 144 per 100000 in men in Golestan in 1990, compared with 8 per 10000 in UK men(4). This review aims to provide a concise review of the most recent epidemiology of OC in Iran (including specific regions), and a discussion of the possible determinants and aetiological factors relating to OC. Due to time and length constraints, this paper will not attempt to use statistical techniques to integrate the results of included studies, and the quality and limitations of individual papers will be assessed only qualitatively.

METHODS

A search of the Ovid MEDLINE database was carried out to identify relevant papers. The MeSH term "Iran" was focussed and combined (AND) with the MeSH term "Esophageal Neoplasms". Each of these terms was combined with plain text searches and with synonyms and alternate spellings and derivations to maximise results. The full search string can be found in Appendix I.

Papers were included only if their study population was in Iran or a specific region of Iran, and if the paper was designed as a case-control or cohort study to investigate the potential reasons for the rates of OC found in Iran. As this is a review of recent literature, papers published before 2000 were excluded, as were papers not in English, preliminary studies or studies where n<100. Although gene-environment interactions may be an important element of OC causation in Iran, consideration of

gene polymorphisms is beyond the scope of this paper and as such, papers relating to this were excluded.

RESULTS AND DISCUSSION

The study selection process returned a total of 94 articles. Of these, 58 were excluded as being irrelevant based on the title alone, and a further 28 were excluded according to the inclusion and exclusion criteria above, as detailed in figure 2. From the included articles, a summary table was created showing their study design, sample size, main findings and strengths and limitations (table 1).

Figure 2 – inclusion flowchart

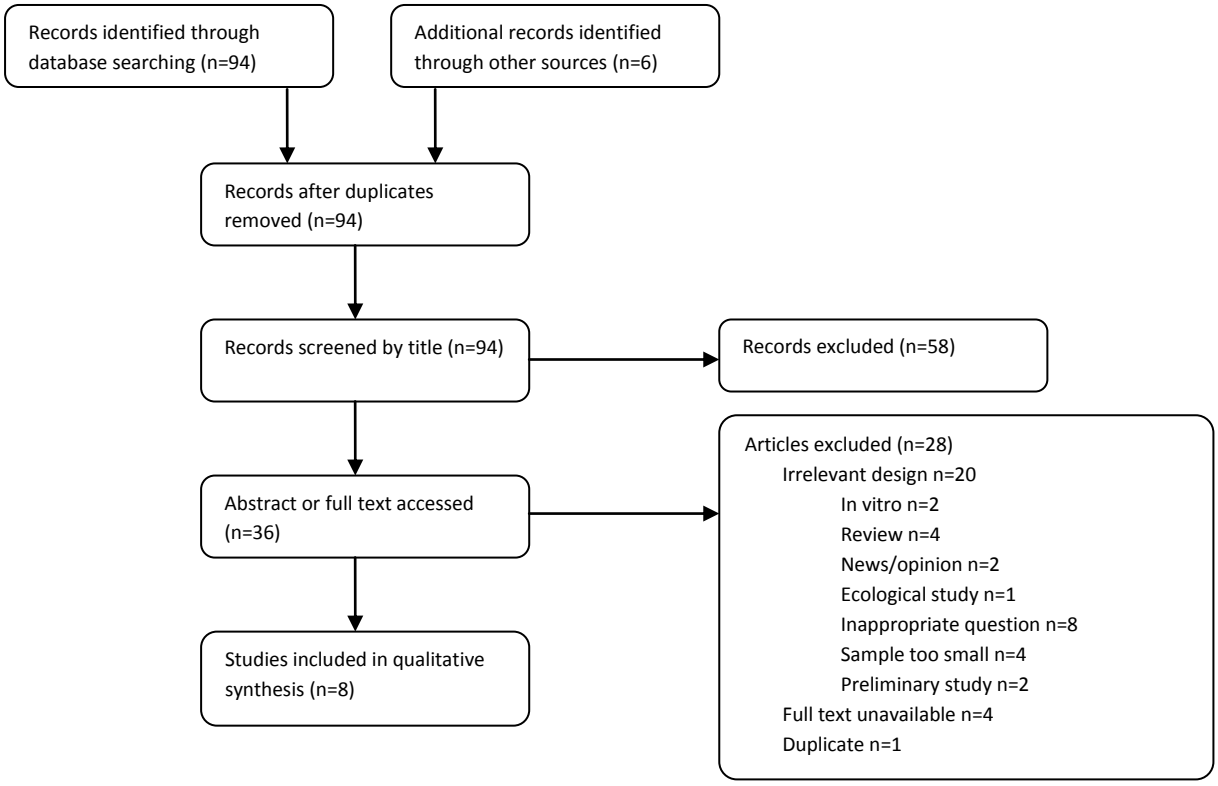


Table 1 – Summary table of included articles.				
Author	**Study design**	**Sample size**	**Findings (95% CI in brackets)**	**Strengths/Limitations**
Khoshbaten M (2011)(7)	**Case-control**	**200**	**"H.pylori infection was strongly associated with a reduced risk of ESCC" (OR=0.28 (0.15-0.54)).**	**Sample size potentially too small to draw meaningful conclusions. Findings contradicted by other studies.**(8)
Nasrollahzadeh D (2011)(5)	**Case-control**	**871**	**Significant association was found between ever opium use (OR=2.00 (1.39 – 2.88)) and OC, but not ever tobacco use (OR= 1.47 (0.98 – 2.21)). Duration and intensity (OR=1.98 (1.20 – 3.25)) of tobacco use was significantly correlated with OC, however. Alcohol showed no association.**	**A large sample size was used and calculations were adjusted for education and ethnicity. However, samples were not adjusted for other known risk factors such as tea drinking and SES. Recall bias (potentially intentional due to the illegal subject matter of the survey) is very possible.**
Pourshams A (2009)(9)	**Cohort**	**16 599**	**The study plans to identify risk factors for OC after collecting data on many different potential risk factors including ethnicity, occupational history, socio-economic status (SES), tobacco, opium and alcohol amongst others.**	**"The GCS is currently too young to provide prospective results regarding the aetiology of OC in Golestan"**
Islami F (2009)(10)	**Case-control**	**871**	**Several measures of SES were significantly correlated with rate of OC, including marriage (OR= 0.41 (0.27–0.63)), house ownership (0.31 (0.13–0.74)), appliance (car (0.53 (0.35–0.81)) and washing machine (0.60 (0.36–0.99))) ownership and primary (0.52 (0.27–0.98)) and secondary (0.20 (0.06–0.65)) education. Results were still significant after adjusting for known direct causes.**	**A large sample size was used and rates were adjusted for confounders including ethnicity, alcohol, tobacco and opium use and vegetable intake. However, correlations obviously do not represent direct causation; measured exposures are only meant as a marker of SES.**
Islami F (2009)(11)	**Case-control and cohort**	**C-C: n=871 C: n=48 582**	**Results for the cohort study were not reported. Results of the case-control study showed: "Compared with drinking warm or lukewarm tea, drinking hot tea (2.07 (1.28 to 3.35)) or very hot tea (8.16 (3.93 to 16.91)) was associated with an increased risk of oesophageal cancer".**	**Strengths are as above (results were obtained from the same study). The data analysed in this study, however, are more subject to information/recall bias.**
Abnet C (2008)(12)	**Case-control**	**943**	**The study found cases compared with controls conferred an odds ratio of 2.10 (1.19-3.70) for having 32 decayed, missing, or filled teeth compared with ≤15. Daily tooth brushing (compared with practicing no regular oral hygiene) was also significantly related to OC with an odds ratio of 2.37 (1.42-3.97).**	**Large sample size; odds ratios were adjusted for known confounders (e.g. smoking and SES) and results were still significant.**
Akbari M (2006)(13)	**Case-control**	**367**	**A significantly increased rate of first degree relatives with OC were found in cases of OC compared to controls (OR=3.6 (2.3–5.7)). An increased rate of consanguinity was also found in cases.**	**All diagnoses were by endoscopic and pathologic evaluation. However, a relatively small sample size was used. Furthermore, the discussion implies this inheritance is genetic; however, this does not necessarily follow – this association could be due to many different confounders. Also, the ethnic makeup of the cases and controls was significantly different; although when this was adjusted for, the association was still significant. The methodology is also fraught with difficulty as it relies heavily on recall, often of details of deceased family**

				members.
Sepehr A (2005)(14)	**Case-control**	**174**	**An association between oral health and occurrence of OC was found with a dose-response relationship; those with a dental prosthesis were significantly more likely to have OC (OR=4.76 (1.48-15.31))**	**Diagnoses were made by reliable methods (histology and endoscopy). However, a small sample size was used and ORs were only adjusted for age, sex and ethnic origin.**

From the included studies, the two most commonly addressed associations were oral health and social and economic status (SES). Other correlations noted included presence of H. pylori, hot tea drinking, opium and tobacco use and familial history of OC.

Oral health

An association between oral health and OC was discussed by two of the reviewed papers(12,14). Abnet et al. (2008) found significant association between having 32 decayed, missing or filled teeth (DMTF) (compared with ≤15) and cases of OC, with an odds ratio of 2.10 (95% CI= 1.19-3.70)(12). There were a surprisingly high number of subjects falling into the DMTF category (42% and 34%). This, coupled with the relatively narrow confidence interval, make this a reliable finding of association. A similar association was found with daily tooth brushing (compared with practicing no regular oral hygiene)(12) and these finding were mirrored by Sepehr et al. (2005), who found those with a dental prosthesis were significantly more likely to have OC (OR=4.76 (1.48-15.31))(14). Due to its smaller sample size, this study has an accordingly wider confidence interval and it also fails to adjust for basic confounders such as smoking and SES. However, Abnet et al. did adjust for these, thus making these findings more plausible.

Although these correlations are convincing and may be useful in policy-making, causation is not by any means implicit. Sepehr et al. discusses some possible mechanisms to explain the correlations found, including physical irritation of the oesophageal epithelium by un-chewed food. However, it is equally likely that oral health may just be a general marker for healthcare-seeking behaviour, or another more direct causative factor. A further study adjusting for all possible confounders would be useful to determine whether this association is in fact directly causative, as suggested by Sepehr et al.. Only then could interventions to reduce OC in Iran be targeted at the correct causative factor.

Social and economic status

Social and economic status was evaluated by two studies(9,10). Unfortunately, the large cohort study headed by Pourshams *et al.* is as yet too young to have yielded any useful results with regards to SES, and the publication included is only a description of the methods of the study so far.

However, a relatively well-designed case-control study by Islami *et al.* was also included in this qualitative synthesis. This study used a reasonably large sample of 871 to test for association between OC and various measures of SES, including education, marriage, appliance ownership and house ownership. Associations were adjusted for many direct causes for which there is already evidence of correlation (such as ethnicity, alcohol, tobacco use, opium use and vegetable intake) and the study still found association between various markers of SES and oesophageal cancer, the most significant being secondary education (OR=0.20 (0.06–0.65)). Since secondary education in itself is unlikely to reduce the prevalence of OC, this implies there are direct causes at play, secondary to SES, for which, as yet, there is no evidence, or which were not adjusted for (for example, oral health).

This finding is important for the directing of future policies and initiatives which may aim to reduce OC rates in Iran, firstly because this study shows that SES is significantly associated with OC, and secondly because it illustrates the need to identify the direct causes which are secondary to SES. These could be improved access to healthcare, or simply better education of when health care attention should be sought.

Other associations addressed

Each of the associations discussed herein were only assessed by one study in this literature review, so they shall be discussed together, in order of strength of evidence.

Islami et al. (2009)(11) published in the BMJ a study on the possible association of tea drinking with OC. This study had many strengths, including a large sample size (n=871) and adjustment for many confounders, including ethnicity, daily vegetable intake, alcohol consumption, tobacco or opium ever use, and various measures of SES. The study found cases of OC were more likely to drink hot or very hot tea than controls (ORs of 2.07 (1.28 to 3.35) and 8.16 (3.93 to 16.91), respectively). These findings were mirrored when the time between pouring and drinking was used as the measured variable. However, the subject matter of this study is very much subject to recall bias and as such, cases may be more likely to recall drinking hot tea than controls. Nevertheless, this study is relatively strong evidence that hot tea drinking is associated with OC. The authors of this study also mention that a cohort study has been set up and will be reported in due course. The findings of this cohort study will be very interesting as it will eliminate much of the issue of recall bias and will give a truer estimate of the risk tea drinking poses, paving the way for primary prevention initiatives targeting this specific cause to be introduced.

A larger problem in terms of recall bias is presented in a study by Nasrollahzadeh et al. (2008)(5). This study identified duration and intensity of tobacco use, and cumulative opium use as significant correlates with OC occurrence. The number of subjects whose cumulative opium use was above the median was significantly higher in cases than in controls (OR=2.34 (1.45 – 3.78)) and the same was shown for intensity of tobacco use (1.98 (1.20 – 3.25)). No significant association was found with alcohol use, although there were very few alcohol users in the sample (only 21 subjects). It appears that the sample used was the same as that used in the 2009 study by Islami et al., therefore the strengths mentioned in the discussion of that study also apply to this study. However, this also suggests that many variables were investigated, and not all of them may have been reported. This is also evidence to suggest that confidence intervals should have been adjusted for multivariate analysis, which there is no evidence of. Also, as mentioned above, the subject matter of this study is somewhat more sensitive, and therefore the potential for (intentional) recall bias is much higher. Whilst this is obviously unfavourable, there is realistically no reason that this bias should affect controls more than cases, and so its importance may be seen as minimal. Therefore, this study is reasonably good evidence for an association between OC and tobacco and opium use. Clearly, the benefits of interventions to reduce smoking and drug addiction are many-fold, and this study further compounds the evidence of this.

A study in 2006 by Akbari et al.(13) investigated the association of familial history of OC with cases of OC in a case-control study. Interestingly, the study chose not to match controls by ethnic subgroup, which is likely to be a major confounder, as shown by the significant difference in ethnicity between cases and controls. However, when ethnicity was adjusted for, a significant association was still found. A significantly increased rate of first degree relatives with OC were found in cases of OC compared to controls (OR=3.6 (2.3–5.7)). Whilst this might suggest a genetic component of causation (as is mentioned in the study), the discussion lacks a mention of the possibility of inherited but non-genetic characteristics. It is possible that risky behaviours (for example, smoking or hot tea drinking) are more likely to occur in an individual whose first degree relatives also partake in these activities, although these are not genetic characteristics. Furthermore, it is stated that 10% of first degree relatives were simply assumed to have suffered from OC “because they suffered from dysphagia prior to death”. This is probably not a valid assumption, and combined with recall bias, works to make this study relatively unreliable in its conclusions. Therefore, whilst there may well be a genetic component to the causation of OC, causing the rates of OC found in Iran, it is not convincingly proved by this study. Further investigation of this may be beneficial, for example to direct screening programmes to genetically susceptible ethnic subgroups.

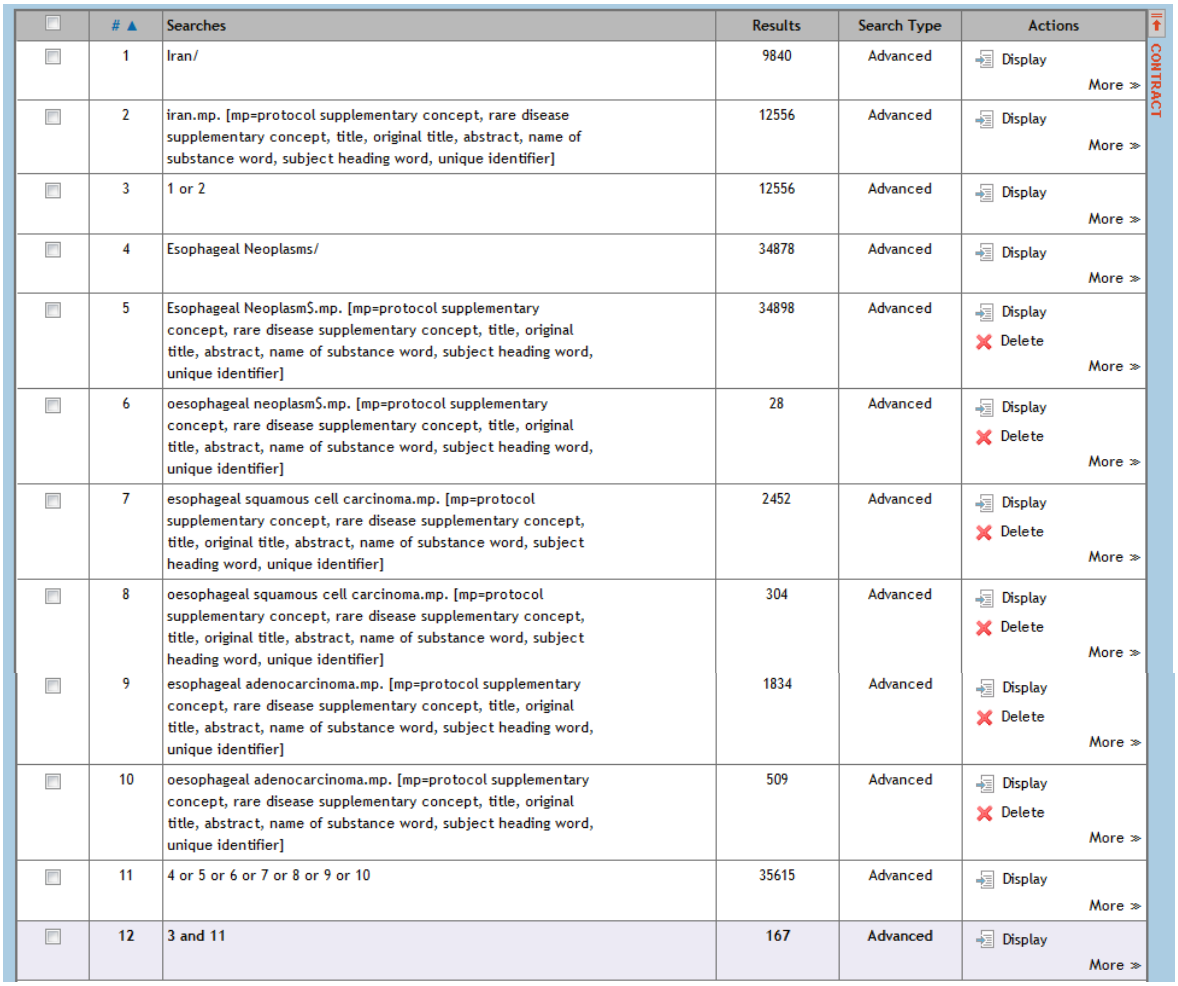
Lastly, a small case-control study was published by Khoshbaten et al. (2011) on the inverse association of Helicobacter pylori and OC. This study found a significantly decreased rate of H. pylori in cases of OC compared with controls (OR=0.28 (0.15-0.54)). Potential mechanisms are discussed for this association, but the paper also cites many studies who have reported no association(8), and even a positive association between H. pylori and OC. The size of sample and the presence of conflicting evidence therefore make this study's conclusions somewhat unstable.

CONCLUSIONS

This review has reported on findings from eight case-control and cohort studies. It has illustrated that much recent research appears to be focussed on the associations of OC with social and economic status and oral health, which, together with the association with hot tea drinking, appear to be the factors with the strongest evidence published since 2000. Future studies will hopefully provide answers to some questions posed by this recent research – in particular, Iran would benefit from further research into the factors secondary to SES which may lead to an increased rate of OC, and also research into the mechanisms which may link poor oral health and OC.

Further studies could aid interventions to reduce OC in Iran by ensuring they are correctly targeted and cost-effective. For instance, it would be both ineffective and cost-ineffective to implement a public health intervention encouraging the population of Golestan to improve their oral health, if it is then found that the association between OC and oral health is not causative, but due to a confounding factor. The same is true for improving rates of secondary education, or introducing smoking cessation services. Indeed, all of these interventions are likely to be beneficial to the population's health for one reason or another, but their efficacy in reducing OC does not necessarily follow. Nevertheless, it may be argued that there is sufficient evidence for some of the associations seen, as well as sufficient collateral benefits to warrant introducing some of the aforementioned interventions at present.

Appendix I – Search string



# ▲	Searches	Results	Search Type	Actions
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2	iran.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	12556	Advanced	Display More »
3	1 or 2	12556	Advanced	Display More »
4	Esophageal Neoplasms/	34878	Advanced	Display More »
5	Esophageal NeoplasmS.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	34898	Advanced	Display Delete More »
6	oesophageal neoplasmS.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	28	Advanced	Display Delete More »
7	esophageal squamous cell carcinoma.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	2452	Advanced	Display Delete More »
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11	4 or 5 or 6 or 7 or 8 or 9 or 10	35615	Advanced	Display More »
12	3 and 11	167	Advanced	Display More »

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