Oral Bisphosphonates and Risk of Cancer
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Bisphosphonates are currently widely used in the treatment and prevention of osteoporosis, as well as in patients with cancer metastases to bone or multiple myeloma. With a 75 million people affected by osteoporosis in the US, Europe and Japan, this represents a significant population being treated with these medications [1]. The benefits conferred by bisphosphonates in terms of reduced mortality and morbidity as a result of fracture reduction are well known, as are some of the adverse side effects such as esophagitis and osteonecrosis of the jaw. However, following a recent report by the US Food and Drug Administration of esophageal cancer in bisphosphonate users, investigators have begun looking at the relationship between the use of oral bisphosphonates and various cancers, especially cancers of the gastrointestinal tract, and have produced varying results [2].

A number of studies [3-5] as well as a meta-analysis [6] of all available studies to date showed a positive relationship with esophageal cancer, which is perhaps not entirely surprising considering the association of oral bisphosphonates with esophagitis. Perhaps less expected is the reduced risk of colorectal cancer and breast cancer associated with bisphosphonate use reported by several investigators. Considering, the wide use of bisphosphonates [7-10], the possibility of an association with cancer development, especially the potential for a protective effect is intriguing.

Bisphosphonates are known to be associated with esophagitis, and patients are given specific instructions on taking the tablets to specifically avoid this complication by aiming to reduce the contact between the tablets and the esophageal lumen (for example, patients are told to take the tablets with water, and to not take them immediately before lying down). Recently however, an association has been made not only with esophagitis, but with esophageal cancer, with 23 cases of esophageal cancer being reported by the US Food and Drug Administration between 1995 and 2008 in users of the bisphosphonate alendronate, and 31 cases in patients using bisphosphonates in Europe and Japan [2]. Since then, several investigators have explored the relationship by looking through existing data registries. Two studies, Cardwell et al. [11] and Green et al. [3] both derived their results from the UK General Practice Research Database but arrived at different conclusions, with Green et al. [3] finding a statistically significant increase in risk of esophageal cancer, but Cardwell et al. [11] find no association. This could be due to the differences in study methodology, and it is possible that the Green et al. [3] study, looking at more esophageal cancer cases over a longer follow-up period, had more power to detect small differences. Interestingly, neither study found an association in patients with a short-term exposure (less than 1 year of 1-3 years), but Green et al. [3] did find an increased risk associated with longer duration of use, a finding confirmed by a meta-analysis [6] of the current observational studies. It has been postulated that the predisposition to cancer of the esophagus occurs through permanent damage to the esophageal mucosa caused by bisphosphonate tablets, remains of which have been found at biopsy in patients with esophagitis [12].

Cardwell et al. [7] reported reductions of 20% and 25% in breast cancer and colorectal cancer risk in bisphosphonate users, respectively. The colorectal cancer finding is supported by other studies, and if the association is real, this is an exciting finding considering that both cancers are common [8-10]. The mechanism of action by which bisphosphonates could protect against colorectal cancer is only speculative at this stage. However, typically less than 1% of an oral bisphosphonate dose is absorbed, with the remaining 99% passing through to the colon, and it has been suggested by Pazianas et al. [13] that bisphosphonates could act locally to disruption the cytokinetic integrity in colorectal cancer cells, leading to apoptosis of these cells. Associations between oral bisphosphonate use and other cancers of the gastrointestinal tract, such as pancreatic or gastric, have not yet been found.

This is an exciting new topic, and with studies appearing in the literature only in the last two years, it will be interesting to follow future developments. A published protocol by Vinogradova et al. [14] indicates that there will be a third study using the same UK data as Cardwell et al. [11] and Green et al. [3] to analyse the relationship with esophageal cancer, and it will be interesting to compare their results to the existing studies. Ideally, the strongest evidence would come from a randomized control trial. However this may not be practical considering the long follow-up times that would be required to observe cancer development and the large cohorts that would be needed to study a rare cancer such as esophageal cancer which has age-standardized incidence rate of 6.5 for males and 1.2 for females per 100,000 in developed countries. Positive associations may lead to recommendations of "drug holidays" and decreased duration of use of bisphosphonates, and protective associations would confer an unexpected benefit to an elderly population in whom bisphosphonates are indicated, and who due to their advanced age are simultaneously at increased risk for the development of colorectal and in the case of female patients, breast cancer. Further studies exploring other gastrointestinal cancers could also possibly uncover further associations not yet reported.

References


