



Research Article

# The Role of the Bracken Fern in Upper Gastrointestinal Tract Malignancies: A Systematic Review of the Evidence

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## Abstract

**Background:** The multifactorial origin of upper alimentary tract cancers encompasses environmental factors mainly associated with diet. *Pteridium aquilinum*—bracken fern—is the only higher plant known to cause cancer in animals. Its carcinogenic toxin, ptaquiloside, has been identified in milk of cows and groundwater. Humans can be directly exposed by consumption of the plant, contaminated water or milk, and spore inhalation.

**Methods:** In order to determine the association between bracken and upper alimentary tract cancers a systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science.

**Results:** Original data was abstracted from each study, the pooled odd ratio and confidence intervals were not calculated as there was no comparable data. However, each study showed a substantial increased risk associated with bracken fern.

**Conclusion:** The current medical literature suggests a serious risk to human health from bracken, and increasing media coverage of the subject is likely to lead to greater education and prevention strategies. Further epidemiological studies are required.

**Keywords:** bracken; gastrointestinal cancer; esophageal cancer; gastric cancer; fern

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## Introduction

The incidence and mortality from cancer of all types in the United States has decreased during the 1991–2006 timeframe.[1] However, the opposite is true for oesophageal cancer. Its incidence and mortality continue to rise. In 2010, estimated new cases of oesophageal cancer number 16,640 in the United States, while deaths total 14,500.[1]The United States has seen an average increase of 20.6% per year in the incidence of adenocarcinoma of the oesophagus since that time[2]. This translates into a 463% and 335% increased incidence in white males and females, respectively, between 1975 and 2004. Adenocarcinoma now accounts for 58% of all oesophageal cancers in the United States. Total oesophageal cancer incidence and mortality have been increasing among white men, stable among white women, and decreasing in black men and women[3]. It is projected that there will be 16470 new patients diagnosed with oesophageal cancer and 14280 deaths from it in 2008[1].

Stomach cancer is one of the most common cancers worldwide, affecting 800,000 new individuals annually. Although its incidence and mortality rates have gradually decreased in the last decades, it remains an important public health problem worldwide, being the second leading cause of cancer deaths.[4] Gastric cancer is thought to result from the interplay of risk factors, among which *Helicobacter pylori* infection plays a major role in combination with environmental factors present in the human diet[5].

Bracken fern is the only higher plant known to cause cancer naturally in animals. Several naturally occurring toxins found in plants have been deemed responsible for animal and human diseases. Among them is the ubiquitous *Pteridium aquilinum*-bracken fern (BF), known to be the cause of acute or chronic toxic syndromes of livestock and the only plant recognized to naturally cause cancer in animals[6, 7]. A nonsesquiterpene compound: ptaquiloside (PTA) has been demonstrated to be the major carcinogen of *P. aquilinum*[7-9]. PTA is transformed to pterosin B (PTB) in acidic solution. Under alkaline conditions, it can form an unstable dienone, which is immediately converted to PTB[7]. The ability of PTA and its derivatives, such as dienone, to induce DNA damage and mutations has been reported previously [10, 11]. PTA has been shown to be present in the milk of cows fed with BF [12]. Humans can be exposed to *P. aquilinum* either directly by eating the plant as in some oriental cultures or indirectly by the consumption of contaminated milk or water or by spore inhalation [13, 14].

This study reviews the bracken-cancer connections established by epidemiological studies in various parts of the world, and provides insights into the possible bridges for bracken carcinogens to reach the human diet.

## Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review[15]. We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to June 2015. The search terms included “gastric cancer”, oesophageal cancer AND “bracken fern”, which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

### Study Selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with upper alimentary tract cancers and their relationship with bracken.

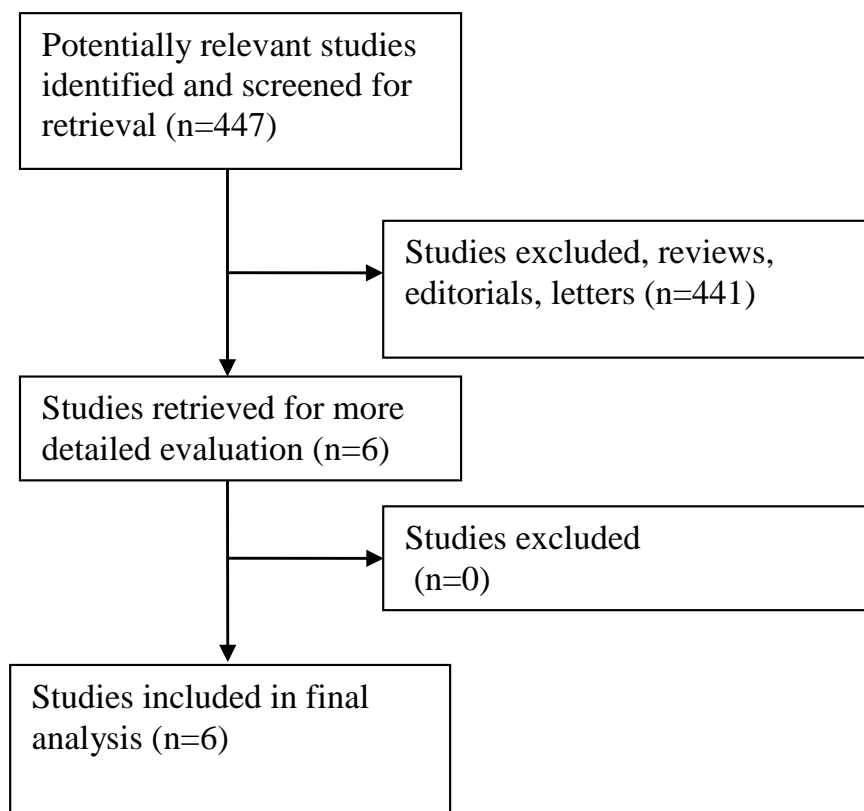
### Data Extraction

We performed the data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data.

## Results

The literature search returned 447 articles. Of these, 441 articles were excluded because they did not meet the pre-defined inclusion criteria. Full texts of the remaining 6 relevant publications were retrieved and examined based on the pre-defined inclusion criteria (Figure 1).

**Figure 1.** Flowchart of studies included in the systematic review.



The studies were from various parts of the world and occurred over various time points, with the first study published in 1975 and the most recent in 2002. Unfortunately, many of the studies did not provide 95% confidence intervals and therefore the data could not be pooled (Table 1).

**Table 1** Study characteristics and results of studies included in the systematic review.

Author	Year	Region of study	Odds ratio
Cuello et al[16]	1976	Nariño, Colombia	2.10
Galpin et al[17, 18]	1989,1990	Gwynedd, Wales	2.52
Villalobos-Salazar et al[19]	1985	Costa Rica	2.62
Hirayama et al[20, 21]	1975,1979	Central Japan	2.68
Marlière et al[22-24]	1998,2000, 2002	Ouro Preto, Brazil	3.63
Alonso-Amelot 2001[25]	2001	Western Venezuela	3.64

## Discussion

### *Upper Alimentary Tract Malignancies and Bracken*

The *BF P. aquilinum* is among the most common plants on the planet. However, it is of public health concern for humans who can be directly exposed. *P. aquilinum* and its PTA toxin have been demonstrated to cause upper digestive tract carcinomas and urinary bladder tumors in cattle. In rodents, exposure to BF leads to leukemia and gastric solid tumors in mice and ileum, urinary bladder, or mammary cancer in rats [26].

The area of Gwynedd in Northern Wales is among the various parts of the UK deeply affected by bracken overabundance. A first survey there [18] found that the longer the duration of residence of people in areas of dense bracken growth, the greater the risk of dying from gastric cancer. Thus, for those with 60 or more years of residence in the area, the risk of dying from this disease was more than twice (OR = 2.52) the risk of those of comparable age living 20 years or less in the community, a statistically significant figure ( $p < 0.05$ ). More importantly, for those exposed to bracken in childhood the risk of developing gastric malignancies was 2.34 ( $p < 0.001$ ) as compared with nonexposed youngsters [17]. These observations are in agreement with the finding that a major component of gastric cancer risk is determined early in life [27, 28]. Well water consumption and gastric carcinomas have been strongly correlated in southern Colombia [16] where incidence of the disease is particularly high, but the cause was attributed to elevated levels of nitrites and nitrates in subterranean waters, not to bracken leachates. In Wales, additionally, the expected relationship of exposure to fern spores depending on occupation and cancer onset could not be established from the available data.

A quite revealing epidemiological study was conducted in Costa Rica[19] which exhibits the highest gastric cancer rates in the Americas and one of the highest in the world for reasons not completely understood. Beef export is an important industry there and pasture overgrazing is relatively common. Intervened land has been shown to be ideal for natural bracken take-over [29] so there is an overabundance of the fern in pasture grassland, especially along the central cordillera where the temperate weather is more appropriate for its growth than the steaming lowlands. In this study, a map of Costa Rica was constructed to examine the possible geographical overlap between active pastureland affected by bracken infestation, BEH and the distribution of gastric cancer by district according to earlier estimates[30]. A later study[31] found that as much as 10% of over 600 slaughtered bovines stemming from one of those central cantons (Perez Zeledón) was affected by BEH. As far as human cancer in these parts, this study also focused on comparing the frequency rates of neoplasia of the upper alimentary tract in high altitude regions –where bracken abounds- and low lying areas where bracken is less abundant. Odds ratios were 2.50 (females) and 2.73 (males).

Along similar lines, an investigation[25] covering the statistical records between 1986 and 1996 of 5.5 million people living in 93,000 Km<sup>2</sup> of topographically contrasting regions of western Venezuela –about twice the area of Costa Rica- revealed striking differences in gastric cancer death rates and geographical location. Other cofactors possibly influencing the observed rate differences were considered, such as poverty levels, nitrates in drinking water supplies, basic nutrients and vitamin load in the diet, availability of medical services, and indirect evidence of *Helicobacter pylori* infection, a known gastric cancer etiological agent. This was assessed by the incidence of gastritis, one of the consequences of the disease. However, none of these factors appeared to contribute as the populations under comparison were quite similar in these components. However, the *H. pylori* morbidity is under a much deeper investigation at present using serum immunoassay techniques and gastric endoscopy of selected, non-symptomatic populations in western Venezuela.

The University of Porto[32] suggested that the genotoxicity of *P. aquilinum* and ptaquiloside, including DNA damaging effects and DNA damage response, was characterized in human gastric epithelial cells and in a mouse model. In vitro, the highest dose of *P. aquilinum* extracts (40 mg/ml) and ptaquiloside (60 µg/ml) decreased cell viability and induced apoptosis. γH2AX and P53-binding protein 1 analysis indicated induction of DNA strand breaks in treated cells. P53 level also increased after exposure, associated with ATR-Chk1 signaling pathway activation. The involvement of ptaquiloside in the DNA damage activity of *P. aquilinum* was confirmed by deregulation of the expression of a panel of genes related to DNA damage signaling pathways and DNA repair, in response to purified ptaquiloside. Oral administration of *P. aquilinum* extracts to mice increased gastric cell proliferation and led to frameshift events in intron 2 of the P53 gene. The data demonstrate the direct DNA damaging and mutagenic effects of *P. aquilinum*. These results are in agreement with the carcinogenic properties attributed to this fern and its ptaquiloside toxin and support their role in promoting gastric carcinogenesis.

## Conclusion

The data published so far supports an important role of bracken in the oesophageal and gastric carcinogenesis process in *P. aquilinum*–exposed populations. As oesophageal and gastric cancer are of multifactorial origin, these results also pave the way to the analysis of synergistic effects of *P. aquilinum* with other high-risk factors for oesophageal and gastric cancer development in exposed populations.

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