Annals of Epidemiology 23 (2013) 762–770

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Consumption of red and processed meat and risk for esophageal squamous cell carcinoma based on a meta-analysis

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ARTICLE INFO

Article history:
Received 4 March 2013
Accepted 30 September 2013
Available online 5 October 2013

Keywords:
Esophageal squamous cell carcinoma
Meta-analysis
Red meat
Processed meat

ABSTRACT

Purpose: To provide a quantitative assessment of the association between red and processed meat intake and the risk of esophageal squamous cell carcinoma (ESCC), we summarized the evidence from observational studies.

Methods: Relevant studies were identified in MEDLINE and EMBASE until October 31, 2012. Summary relative risks with 95% confidence intervals (CIs) were pooled with high versus low and linear dose-response random-effects models.

Results: A total of 21 studies (19 case-control and two cohort studies) with 6499 ESCC cases were included in this meta-analysis. Based on high versus low analysis, the summary relative risks of ESCC were 1.57 (95% CI, 1.26–1.95; $P_{heterogeneity} = .003$, $I^2 = 56.0\%$) for red meat intake and 1.55 (95% CI, 1.22–1.97; $P_{heterogeneity} = .029$, $I^2 = 45.3\%$) for processed meat intake. Subgrouped and sensitivity analyses revealed that the increment of ESCC risk with intakes of red meat and processed meat was stable and robust. These results are consistent with the results of the dose-response analyses. There was evidence of a nonlinear association of processed meat intake and ESCC risk ($P_{nonlinearity} = .019$).

Conclusions: Intake of red and processed meat may be associated with significantly increased risk of ESCC. Further investigations with prospective designs are warranted.

Introduction

Esophageal cancer (EC) ranked the eighth most frequently diagnosed cancer and the sixth most common cause of cancer mortality in the world, with an estimated 482,000 new cases and 407,000 deaths in 2008 [1]. EC includes two major forms, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Recently, a dramatic increase in the incidence rate of EAC has been noticed in the United States and Western Europe, along with a decrease in the incidence rate of ESCC [2,3]. However, ESCC is still the most common histologic type of esophageal cancer worldwide, particularly in high-risk areas such as China and Iran, where it accounts for about 90% of the total esophageal cancer cases [4–6].

Identification of epidemiologic factors may facilitate prevention and/or early detection of this disease. Results to date indicate that tobacco smoking and alcohol consumption are the most known risk factors for ESCC development [7,8]. In addition, diet and dietary carcinogen exposure (such as *N*-nitroso compounds [NOCs], heterocyclic amines [HCAs], and polycyclic aromatic hydrocarbons [PAHs]) seem to play a major role in the pathogenesis of this neoplasia among high-risk populations of developing countries [9].

Epidemiologic studies have explored the association of intake of red and processed meat and risk of ESCC with inconsistent results [10–20]. In 2007, the Working Group from the World Cancer Research Fund/American Institute for Cancer Research concluded that no recommendation could be reliably made regarding intakes of red meat and processed meat and EC risk [21]. Since this report was published, a lot of important epidemiologic studies, especially two prospective cohort studies: the NIH-AARP Diet and Health study [13] and the Netherlands Cohort Study [20], have been published and have yielded inconsistent results. In addition, no distinction was made in that report between ESCC and EAC, which are distinct in etiologic and pathologic characteristics. Importantly, the exact shape of the dose-risk relationship between red and processed meat intake and ESCC risk has not been clearly defined.

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http://dx.doi.org/10.1016/j.annepidem.2013.09.003

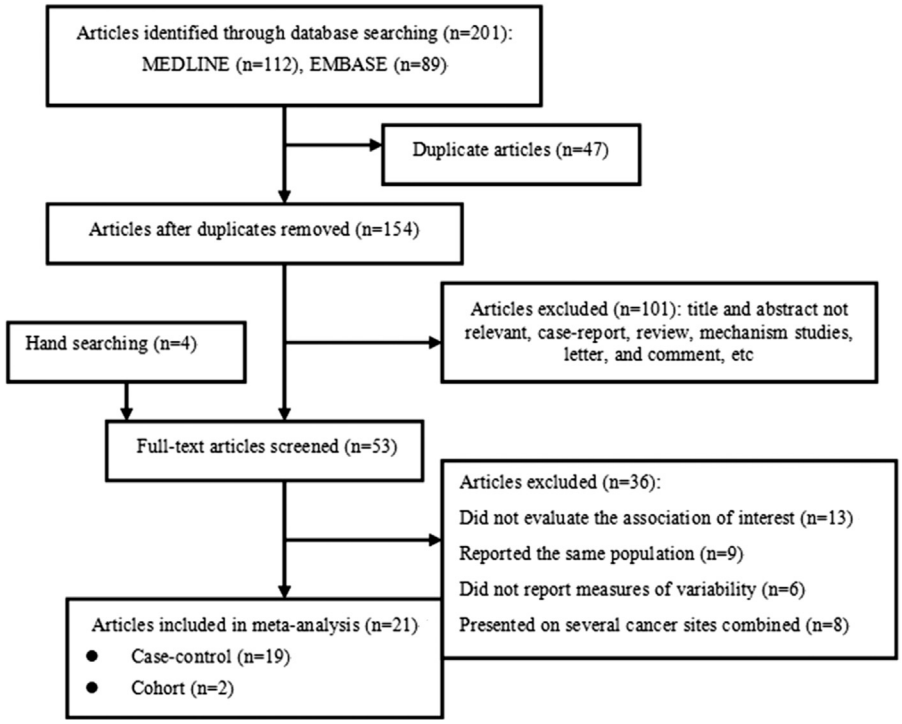

Fig. 1. Flow diagram of systematic literature search on red and processed meat intake and the risk of ESCC.

Therefore, to better characterize this issue, we conducted an updated and comprehensive meta-analysis of the current epidemiologic literature following the Meta-analysis Of Observational Studies in Epidemiology guidelines [22].

Methods

Data sources and searches

A computerized literature search was conducted in MEDLINE (from January 1, 1966) and EMBASE (from January 1, 1974), to October 31, 2012, independently by two investigators (Q.X.D. and B.Q.W.). We searched the relevant studies with the following text word and/or Medical Subject Heading terms: (1) (o)esophageal OR (o)esophagus; (2) cancer OR carcinoma OR neoplasia; and (3) red meat OR processed meat OR preserved meat OR beef OR pork OR veal OR mutton OR lamb OR ham OR sausage OR bacon OR salted meat. Furthermore, we reviewed the reference lists of the relevant articles to identify additional studies. No language restrictions were imposed.

Definition of exposure and outcome

The definitions of red and processed meat varied across studies. In the current meta-analysis, red meat was defined as the intake of beef, veal, pork, lamb, or a combination thereof [23], and processed meat was generally defined as the meat made largely from pork, beef, or lamb that undergoes methods of preservation, such as curing, smoking, salted, or drying [23].

When studies reported outcomes according to histologic subtypes of EC, we only extracted and pooled relative risks (RRs) for ESCC. For studies that did not report subtype-specific risk estimate, we assumed that the majority of EC cases from non-Western countries were ESCC [24]. As the rise in the incidence of adenocarcinoma in Western countries mainly occurred in the most recent decades [24], we excluded Western studies that initiated after 1990 and did not report on histologic subtypes. We included the study by Levi et al. [25] because 92 ESCC cases of 101 EC cases were recruited in this study.

Study selection

To be included in our meta-analysis, studies had to (1) be published as an original study; (2) use a case-control, nested case-control, or cohort design; and (3) be reported as point estimates (i.e., rate ratios, odds ratios) and measures of variability (i.e., 95% confidence intervals [CIs]) for red and/or processed meat intake and the risk of ESCC at least adjusted for age or provided an RR with corresponding 95% CIs per unit increment in red and/or processed meat intake. Non-peer-reviewed articles, ecologic assessments, correlation studies, animal studies, and mechanistic studies were excluded. Studies were excluded if they reported on several cancer sites combined, for example, upper aerodigestive tract cancers or cancers of oral cavity, pharynx, and esophagus combined. Studies that reported data for a broad classification of meat, such as “total meat” categories, which included poultry or fish, were excluded. If data were duplicated in more than one study, the most recent or informative studies were included in this analysis.

Data extraction

Where data were available, two researchers (Q.X and J.Y.) independently extracted information on the first author’s last name, year of publication, geographic locations, sources and number of controls for case-control studies, methods of ascertainment of dietary variables, number of cases, comparison of exposure level (the highest category vs. lowest one), duration of follow-up for cohort studies, adjustments for confounders, and the RR estimates with corresponding 95% CIs for the highest versus lowest level. For