Review

Diet and cancer: Risk factors and epidemiological evidence

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ABSTRACT

Background: Diet represents 30–35% of risk factors that contribute to the onset of cancer. Some foods and dietary patterns have been linked to the risk of various cancers. However, epidemiological available data are not consistent for many foods and the associations with cancer risk remain unclear. The concerns about this issue are considered like a “Hot topic” for oncologists and general population.

Objective: The aim of this report is to present a review of the published epidemiologic research to date reflecting the most current scientific evidence related to diet and cancer risk.

Design: EMBASE and PubMed-NCBI were searched for relevant articles up to October 2013 that identified potentials interactions between foods or dietary patterns with cancer risk.

Results: There is no conclusive evidence as an independent risk factor for isolated nutrients versus adoption of dietary patterns for cancer risk. Moderate physical activity after breast cancer diagnosis contributes to 40% reduction of recurrence/disease-specific mortality. Cancer colon risk derived from meat intake is influenced by both total intake and its frequency. The interaction of phenolic compounds on metabolic and signaling pathways like P450, MAP kinase, PI3 kinase, IGF-1, NF-kB and ROS seems to exert an inhibitory effect on cell proliferation and tumor metastasis and induces apoptosis in various types of cancer cells, including colon, lung, prostate, hepatocellular or breast cancer.

Conclusions: There is a direct relationship between unhealthy diet and lifestyle with the increase of tumor development and cancer risk. For this reason, a good nutritional status based on a balanced diet constitutes one of the main preventive factors from tumors. However, the mixed results from epidemiologic studies hinder to get unequivocal and consistent evidence about the interaction between diet and cancer risk. More epidemiological studies will be needed in the future to clarify this issue.

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http://dx.doi.org/10.1016/j.maturitas.2013.11.010
Introduction

Exhaustive study of the factors that contribute to the onset of cancer has determined that genetic factors account only for 5% of tumors, while 95% is due to environmental factors [1], encompassing as pivotal pillars lifestyle (tobacco, alcohol, physical activity), external stimuli (radiation, pollution, infections, etc.) and diet [2].

Diet represents 30–35% of risk factors, warranting the efforts made by different international organizations and institutions like World Cancer Research Fund (WCRF) or American Institute for Cancer Research (AICR), and the collaboration of investigators all around the world, that initiate studies aimed to broaden our knowledge about the relationship between dietary risk factors and tumor development.

Although first epidemiological studies investigating the causal relationship between diet and cancer began several decades ago, we found the higher number of well-designed studies conducted during the last decade, that have obtained reliable and plausi-
ble data. Many of the previous studies presented important bias including reductionist designs (i.e., effect of one nutrient or particular food), design bias in questionnaires, increase or decrease in tumors endpoints, etc. Despite the existing bias, we have now deeper knowledge about the mechanisms and pathways implicated in tumor onset and development; however, the global positive or negative impact of particular risk factors has not been determined using certain approaches focused on “isolated nutrients” instead of “dietary patterns” [3].

From an epidemiological point of view, food and nutrients are not ingested alone, and there is a possible interaction between them. Using a comprehensive model of study, search of certain dietary patterns is warranted instead of individual evaluation of a particular food or nutrient that could positively or negatively affect the risk of cancer development [4].

Classifications of dietary patterns could present little variations between studies but globally they agree on the following features:

(i) Healthy pattern: diet with a high content of fruits, vegetables, poultry, fish, whole grain cereals and a low daily intake of fats.

(ii) Unhealthy pattern: diet with high content of red meat and/or processed meat, refined sugars, potatoes, sweet foods and a high daily intake of fats.

(iii) Drinker pattern: diet with a high content of wines, beers and liquors.

Some studies have demonstrated a risk reduction of breast cancer (mean reduction of 11%) in women that have a good adherence to the healthy pattern criteria. In contrast, women with a predomin-
ant drinker pattern show an increase of risk of breast cancer (up to 21%) when the degree of adherence is evaluated.

Research in these dietary patterns has also shown associations between diet and other (chronic) pathologies, including cardiovascular, endocrine or inflammatory diseases. The namely Mediterranean diet is identified by a characteristic pattern consisting mostly of fruits and vegetables, cereals, legumes, olive oil, fish, white meat and dairy products, and a moderate consumption of wine and red meats. Evidence from studies conducted during several decades (in diverse countries with a strong adherence to this dietary pattern) highlights the positive effect of health pattern on decreasing cardiovascular diseases and certain types of cancer [5].

It has been shown that immigrant people adopting new pat-
terns and daily habits from their new location become at risk to factors previously not affecting them. This has been also confirmed among genetically identical individuals (twins) that live in different surroundings [6–9].

This paper aims to review the most current information that we have in relation to the interaction between diet and cancer. The review takes as mainly baseline epidemiological studies published in the last five years, with the aim of identifying risk factors and the degree of evidence thereof. Furthermore special attention to various metabolic pathways and signaling pathways by which various compounds found in foods, potentially interact modifying the relative risk or preventing the development of tumors.

Methods

An extensive review of scientific literature was conducted in EMBASE and PubMed central (PMC)-NCBI to identify human studies written in the English and Spanish language published up to October 2013. The search included the following keywords or phrases: diet, cancer, epidemiology, risk factors, neoplasm and lifestyle. Studies that reported risk estimates [hazards ratios, odds ratios (ORs), and relative risk] of cancer and measures of variability (SEs or 95% CIs from which these could be derived) were selected preferably.

Epidemiological evidence related carbohydrate intake and cancer

One of the imbalance with more rapid onset among the dietary changes occurred in the last decades has been the increase in high carbohydrate food or refined sugars (RCH) intake. This excess derives from the broad variety of processed products, with its prime example in the “fast food” or the pejoratively known as “junk food”, that has a high proportion of RCH and saturated fatty acids.

Improved technology in food industry has achieved the produc-
tion of more tasty food; however, these better organoleptic features are not associated to desirable healthy effects. During the refining process carbohydrates become more concentrated and there is a reduction in macronutrients (proteins and fats) and micronu-
trients (vitamins and minerals), due to vegetable shells removal where their content is higher, for example in whole grain cereals.

In epidemiological studies, two concepts have generated major interest: glycemic load (GL), that measures the amount of carbohy-
drates in a serving of food, and glycemic index (GI), that indicates how rapidly a food is digested and released as glucose (sugar) into the bloodstream.

The growing interest of diet-derived GL and GI roles has a link with the risk of breast cancer development. Although in old epidemiological studies this relationship could not been established or very weakly, recent conclusions from the meta-analysis of cohort studies show a clear association between GI values, RCH post-prandial effects, hyperinsulinemia and increased risk of breast cancer, up to 8% when comparing the lowest range of GI intake to the highest range of GI intake [10]. In other cancer types, such as colorectal cancer, an independent association between diets high in carbohydrate, glycemic index, or glycemic load could not been established [11].

Obesity: the importance of maintaining a healthy weight through physical activity and diet control

Evolution of dietary patterns and lifestyle in most developed countries has increased overweight and obesity prevalence. Obesity, defined as a body mass index (BMI, kg/m²) greater than 30 kg/m², and overweight BMI between 25 and 29.9 kg/m² are associated with increased mortality in colorectal, breast (post-menopausal), esoph-
agus (adenocarcinoma), prostate, endometrial, liver and pancreatic cancers [12–16]. Epidemiological evidence shows some discrepan-
cies related to the association between high fat diets and increased risk of tumors [17]. It has been reported a lack of effect on reduc-
tion of colorectal cancer risk after the adoption of a healthy dietary pattern, low in fat and high in fiber, fruits, and vegetables [18].
In the obesity–cancer relationship, multiple biologic processes participate and there is implication of certain factors such as insulin, insulin-like growth factor (IGF)-1, insulin resistance, sexual hormones (estrogens), pro-inflammatory cytokines (tumor necrosis factor alpha (TNF), interleukine-6) and C-reactive protein (marker of chronic vascular inflammation). The balance and/or interactions between all these factors determine a low or high increase of cancer risk.

One hypothesized mechanism of body fat influence on cancer risk is based on its direct effect on certain hormone levels, as insulin, estrogens and IGF-1, that produces a favorable environment for carcinogenesis and decreases cellular apoptosis [16]. Particularly, abdominal fat increases insulin resistance and subsequent hyperinsulinemia, which increases risk of colorectal and endometrial cancer. Adipose tissue is the main site of estrogen synthesis in men and post-menopausal women, and obese subjects present a similar hormone profile to post-menopausal women regarding estradiol/estrogen ratio, due to the high activity of aromatase and 17-beta-hydroxysteroid dehydrogenase enzymatic systems in adipose tissue, responsible for androgen to estrogen conversion and estrone to estradiol conversion. These biologic processes explain the elevation of free estradiol levels in post-menopausal women, resulting in a proliferative cell action and a more than two-fold increase of breast cancer risk [17]

Estrogens effects (mainly estradiol, very active compared with other endogenous estrogens) vary according to the binding receptor implicated. Thus, it has been shown that estrogen receptor (ER) beta (mostly expressed in non-malignant tissues) mediated-actions do not promote an increase in cell proliferation. In contrast, this proliferative action can be found in pre-tumor tissues, where the alfa subtype of ER could be predominant [15].

Obesity is also related to chronic hyperinsulinemia (due to higher insulin resistance) that leads to an increase of IGF-1 bioavailability. Together with possible cell microenvironment variations caused by present inflammatory molecules (TNF alpha, IL-6, CPR), this contributes to malignant cell proliferation, increased angiogenesis and metastases [19]. Using CPR as a chronic inflammation marker, it has been shown that high CPR levels are associated to a poorer survival in breast cancer patients [20].

Adoption of a healthy lifestyle comprising a Mediterranean diet and moderate physical activity reduces both the incidence [16,17] and recurrence of certain types of tumors after treated at first stages [21].

Regular and moderate physical activity elevates basal metabolism and improves tissue oxygenation, leading to better metabolic efficiency and capacity and finally reducing body fat, insulin levels and insulin resistance. Consequently, physical activity reduces risk of cancer. When different levels of physical activity are compared, the most active women (physical activity >42 h/week) have 25% lower risk of breast cancer than the least active (physical activity <7 h/week) and this association did not differ by ER status or BMI [22]. Thirty minutes daily of moderate exercise result in an 11% reduction of colorectal cancer [16].

Current guidelines for adults recommend at least 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic activity for overall health [23]. Walking on average at least 1 h/day was associated with 14% reduce risk of breast cancer in postmenopausal women [22]. The positive effect of physical activity on reducing risk of tumor development goes beyond what we could identify as a “preventive action”. In women with stage I–III breast cancer, the reported effect of moderate exercise made during 3 years after diagnosis versus a sedentary lifestyle was 30% reduction of total mortality and 40% reduction of recurrence/disease-specific mortality [21]. In contrast, physical inactivity is associated to a status of low grade chronic inflammation or latent inflammation, and higher estrogen, androgen and insulin levels. Insulin stimulates ovarian androgen synthesis and growth hormone receptor expression, and inhibits liver production of binding proteins such as sex hormones binding globulins (SHBG) and IGF-1 binding proteins, leading to a greater bioavailability of circulating estrogens and IGF-1 [24–26].

Omega-3 and omega-6 fatty acids

Essential fatty acids of omega-3 family (alpha-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)) and omega-6 family (linoleic acid and arachidonic acid) have been a lengthy subject of study, because of their nutritional importance and their relationship with the onset of certain types of tumors. In spite of the great number of studies conducted during last decades, current scientific evidence is controversial and lacks consistent conclusions about a possible reduction effect on the risk of tumors in breast, lung, colorectal, bladder or prostate cancer [27].

In the extensive literature on this type of fatty acids (omega-3, ratio omega-3/omega-6) and their association to carcinogenesis, several mechanisms of action have been proposed. One of the most accepted mechanism is based on the relationship between inflammatory pathways and the product compounds resulting from the action of cyclooxygenase 2 (COX-2) upon omega-3 and omega-6 fatty acids. However, metabolic features of these fatty acids are completely opposite. Omega-6 fatty acids are converted by COX-2 enzyme into prostaglandin E2, a pro-inflammatory cytokine that facilitates cell proliferation and angiogenesis, whereas omega 3 fatty acids are substrate for COX-2 enzyme resulting in the production of prostaglandin E3, which does not possess mitogenic properties [28].

This hypothesis could explain the results obtained from the evaluation of the influence of ratio omega-3/omega-6 on melanoma [29], and the effects of oil fish (rich in EPA and DHA) on colorectal cancer [15] or prostate cancer, where the heterogeneity of incidence results generates conflicting conclusions [30,31].

Limit consumption of meat and processed meat

During the last three decades, diversely located epidemiological studies have shown a population change in dietary habits, with an increase of red meat consumption and the associated risk of colorectal cancer [32]. This strong association between meat intake and increased incidence of colorectal cancer has also been demonstrated for bladder, kidney and endometrial tumors [33]. For the analysis of this causal relationship, different product intake can be considered, such us total fresh meat, red or white meats, low or high processed meat (amount of additives), elaboration methods (smoked, cured, salt, etc.) or dietary patterns associated (i.e., meats, fats, vegetables, wine…). There are several pathways or mechanisms of action proposed:

- Increased fat intake together with meat intake. There is an increase in insulin resistance and higher production of secondary bile acids, which facilitates carcinogenesis.
- Heterocyclic aromatic amine (HAA) formation, HAA formation happens during high temperature and/or long-lasting cooking.
- Polycyclic aromatic hydrocarbons (PAH) formation, resulting from incomplete combustion of organic material, such as coal, wood, etc.
- N-nitroso compounds (NOC), produced inside meat per se or by endogenous metabolic processes due to redox reactions of nitrogen oxides, nitrates and nitrates with secondary amines, namely N-alkyl amines.
- Heme iron. Red meats have a high content of heme iron, that behaves as a nitrosylation agent forming NOC, and increases cell
proliferation in gut mucosa through the lipid-peroxidation pathway.

HAA, PAH and N-nitrosamines are considered as genotoxic substances among carcinogenic dietary factors, acting directly on DNA and causing point mutations, deletions, insertions, etc. Beginning in cytochrome P450, the metabolic pathway of these molecules generates reactive metabolites that interact to DNA, thus initiating carcinogenesis process for several cancers such as breast, colorectal, prostate, lung, liver, kidney, stomach, pancreas and bladder cancers [34].

Studies evaluating genetic susceptibility for carcinogenesis have focused on the enzymes implicated on carcinogenic detoxification process and metabolism. Enzyme polymorphisms found (for example, in cytochrome P450, glutathione S-transferase, UDP-glucuronosyltransferase, or N-acetyltransferase) can elevate incidence of tumor onset. Particularly, N-acetyltransferase type 1 and 2 polymorphisms are risk factors for colorectal and bladder cancer [33].

Evidence of the causal relationship between red meat consumption and increased risk of colorectal cancer has been deemed “convincing” by the WCRF/AICR. Recent meta-analysis of cohort studies estimated that consumption of about 100 g of red meat or 50 g of processed meat increases the risk of colorectal cancer by approximately 15–20% [35]. It is also important to determine both intake amount [36] (for a dose–response analysis) and intake frequency [37].

International epidemiological studies with a high number of participants show that risk of colorectal cancer can increase 35% in people taking up to 160 g/day of meat compared to subjects taken less than 20 g/day. In cases of processed meat consumption, this risk can arise up to 48% with an intake of 25 g/day [33]. In studies analyzing the rise of risk in relation to the total intake of meat (red and/or processed meat), colorectal cancer risk increases in a nonlinear manner up to 22% with intakes from 20 g/day to 140 g/day, then the increase becomes stable [36]. Specific results of risk of pancreatic cancer in smoker women show a 38% of increase with 1 mg/day of heme-iron intakes [38].

Meat intake frequency also has an effect on the increase of risk of colorectal cancer. When intake is more than once a day, risk increases up to 37% for colorectal cancer and 43% for rectal cancer, versus 21% when intake is 50 g/day at once [37]. This can be explained by the continued production of bile acids cause by repeated intake of meat.

Despite the strong association of meat intake with increased risk of colorectal cancer found in epidemiological studies [39] it is important to note that some meat components are anticancer substances and essential for human nutrition (selenium, zinc, omega-3 fatty acids, vitamins B6, B12, D and folic acid). Recommendations for minimizing risk of colorectal cancer are based on decreasing but not eliminating meat intake, and complement with a high fiber diet and practice of physical activity [40].

Fruits and vegetables “cornerstone” of our diet

Benefit provided by a high fruit and vegetable diet not only is present in cardiovascular, chronic or degenerative diseases but it is also evident in other pathologies like cancer, which has been extensively reported. Institutions as WCRF/AICR repeatedly recommend intake of this kind of foods for cancer prevention. The positive effects provided by fruits and vegetables come from the great number of potentially protective substances they content, that affect to different biochemical pathways [41]. Multiple epidemiological studies have investigated the role of polyphenolic compounds, flavonoids, isoflavones, epigallocatechin-3-gallate, lycopene, diallyl trisulfide, isothiocyanates, resveratrol, selenium, beta carotenoinds, vitamins E, D, C, A, B12, B6 and folic acid.

Polyphenolic compounds

A regular consumption of polyphenols through intake of fruits, vegetables and certain plants is associated to a reduction of some chronic, cardiovascular and cancer diseases [42]. Together with their direct antioxidant action, these compounds affect several metabolic pathways [43], such as cytochrome P450 and signal pathways mediated by MAP-kinases, PI3-kinases, IGF-1, NF-κB and ROS, implicated in both normal and pathologic cell function. Phenolic derivatives contribute, then, to cell adhesion processes, migration and tumor angiogenesis [44]. Their beneficial effect can be observed by its inhibitory action at early stages or advanced or metastatic tumor stages. Among most studied polyphenolic compounds we found: resveratrol (high content in red grape), which has activity against lung, breast and prostate cancers, hepatocellular carcinomas, melanomas or glioblastomas; galic acid, against gastric cancer and gliomas; chlorogenic acid, against hepatocellular carcinomas and fibroblastic sarcomas; caffeic acid against hepatocellular carcinomas and prostate and lung cancers [44]. Red fruit flavonoids have positive effects on gastric cancer [45] and pomegranate flavonoids positively affect breast, prostate, colon, cutaneous and lung cancers [46]. Lycopine is good for prostate cancer [47].

Epigallocatechin-3-gallate is a major polyphenol found in green tea. In vitro and in vivo research have demonstrated a preventive action for malignant diseases, but this effect is not clearly observe in the results from epidemiological and intervention studies performed in prostate cancer [48], hepatocellular carcinoma and colorectal cancer [49]. In other types of tumors (esophageal or lung cancer), there is a report of risk reductions of 18% in non-smoker participants, but overall results are not conclusive. Diversity of study populations (occidental or Asiatic) and different dose of tea intake could explain the lack of positive results in humans [50].

Sulfur compounds

Diallyl trisulfide is a characteristic component of garlic and other similar vegetables (onion, leek, chive, etc.) with hypolipidemic and hypoglycemic activity, and is active against cardiovascular and metabolic diseases. Mechanism of action underlying the effect against cancer is not well established, but diallys trisulfide inhibits oncogene production and angiogenesis and enhances metabolic pathways for carcinogenic detoxification and cell apoptosis induction [51,52].

Vitamins and minerals

Vitamins E, C and D and selenium share fundamental antioxidant properties and all fight against oxidative stress and its harmful effects in our organism, leading to carcinogenesis. However, oxidative stress is a natural process with positive actions, such as improving immune response [53]. Although some epidemiological studies have found a benefit of a high fruits and vegetable consumption on prevention for certain types of tumors like cervix uteri [54,55] or head and neck cancer [56], epidemiological evidence available is not completely consistent. There are inconclusive results for vitamins E, C and selenium in hepatocellular carcinoma [57] and prostate cancer [58], for vitamin D and folic acid in pancreatic cancer [59,60] or for group B vitamins in prostate cancer [61].

Isoflavones

Isoflavones are the most studied compounds among flavonoid group, mainly soy isoflavones, characterized by anti-estrogenic activity (they compete specially for beta estrogen receptor), actions
in intracellular metabolism of steroids (inhibiting enzymes implicated in androgen to estrogen conversion) and anti-proliferative, anti-angiogenic and pro-apoptotic activities in tumor cells [62].

There are no clear conclusions regarding a beneficial effect of soy isoflavones. In vitro results show positive effects but case-control studies and phase III clinical trials provide inconclusive results for certain types of tumors like breast or prostate neoplasms [62,63]. In Asiatic women, soy isoflavones achieved a 29% of reduction of breast cancer risk with an intake of 20 mg/day versus 5 mg/day. In contrast, a meta-analysis of studies performed with occidental women did not find any association, although the amount of isoflavones ingested was 0.8 mg/day [62]. This diversity of results can be caused by several factors, such as dose and type of isoflavones, hormonal tumor status or even different enzymatic polymorphisms between individuals [64].

**Fiber**

Fruit, vegetable and whole grain cereals consumption provide the amount of fiber necessary for our organism, of which recommendation ranges between 21 and 38 g/day. Fiber protective effect associated mainly to colorectal cancer is also extensive to other types of cancer. It has been shown a reduction of 11% in risk of breast cancer in subjects with the highest intake of fiber versus the lowest intake of fiber [65]. There is a dose–response relationship, each 10 g/day of increased intake of fiber is associated to 7% reduction of risk, independently of region, ethnic group or menopausal status.

Proposed mechanisms of action for fiber effects on colorectal cancer are shown in Fig. 1, consisting of a series of actions that together could explain the benefits of fiber not only in cancer, but also in diabetes, bowel inflammatory diseases or cardiovascular diseases [66].

Currently, epidemiological evidence is not conclusive regarding the effects of fiber on reduction of colorectal cancer. We can find studies with positive results up to a 25% decrease of cancer risk for intakes between 33.1 g/day and 12.6 g/day, or 17% decrease for intakes of 3 times/day. However, many other studies have not found any beneficial effect [66,67]. Novel approaches for investigating the relationship between fiber consumption and colorectal cancer have been proposed, taking into account dietary patterns and specific aspects such shell of cereals, processing degree of foods, effects on immune system or microbiome composition in the colon [68,69].

**Discussion**

The available evidence confirms that there is a direct relationship between diet, lifestyle and risk of cancer development. It is estimated that up to 35% of risk factors are associated to diet and therefore cancer risk can be modified. Current evidence highlights that cancer is a preventable disease that requires major lifestyle changes (minimal meat consumption, increased ingestion of whole grains, fruits and vegetable, reduce fat intake, practice exercise at least 30 min/day... and if people adopt consistently the healthy patterns throughout their life could represent a decreased likelihood on cancer onset. In addition recent scientific discoveries describes how foods or nutrients affect directly to several metabolic and signal pathways (P450, MAP-kinase, IGF-1, NF-kB, ROS etc.) implicated in both, normal or pathologic cell function. Strong evidence is available for the positive effect of physical activity on lowering the incidence of tumor and even reducing recurrence in patients with cancer already treated (like in breast cancer). The mechanisms through obesity and overweight increase cancer risk are multiple and varied (include effects on immune function and inflammation, levels and metabolism of several hormones and proteins like insulin, estradiol, IGF-1 etc.). There is special interest about the potential effects of single fractions inside some foods like fiber that it has intake recommendation at minimum 20 g/day, not only for their potential protective activity in reducing cancers of gastrointestinal tract but also with lower risk of cardiovascular disease and diabetes [70,71].

The recommendations of major international guidelines (World Cancer Research Fund, American Institute for Cancer Research or American Cancer Society), remain the starting point for designing new epidemiological studies [72,73].

Limitations in the present review should be acknowledged. For many issues concerning diet and cancer, the evidence is not definitive because the published results are inconsistent or because the methods of studying in human populations continue to evolve [73]. The assessment of epidemiological studies itself involve risk bias assumptions because of the studies heterogeneity (relate to dose of a nutritional factor is need to achieve its expected protective effect, error associated with food frequency questionnaires, stage of carcinogenesis on which many nutritional factor act etc.) and mixed results. Further researches will be needed in the future since lack of evidence in some important issues related to diet and cancer risk, remain unclear.

![Fig. 1. Scheme of potential mechanisms of protection of fiber in colorectal cancer. SCA, short-chain fatty acids. Adapted from S. Romanero. Top Clin Nutr. 2012.](image-url)
Centers for Disease Control and Prevention. Division of Nutrition, Physical Activity, and Obesity National Center for Chronic Disease Prevention and Health Promotion. How much physical activity do adults need? Atlanta, GA: Centers for Disease Control and Prevention; 2013 [updated 2011 Dec 1; cited 2013 April 4].


