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Alcohol Consumption and Cancer Risk: Understanding Possible Causal Mechanisms for Breast and Colorectal Cancers

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Disease Control and Prevention (CDC) requested and funded this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by E-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives: The purpose of this report is to systematically examine the possible causal mechanism(s) that may explain the association between alcohol (ethanol) consumption and the risk of developing breast and colorectal cancers.

Data Sources: We searched 11 external databases, including PubMed and EMBASE, for studies on possible mechanisms. These searches used Medical Subject Headings and free text words to identify relevant evidence.

Review Methods: Two reviewers independently screened search results, selected studies to be included, and reviewed each trial for inclusion. We manually examined the bibliographies of included studies, scanned the content of new issues of selected journals, and reviewed relevant gray literature for potential additional articles.

Results:

Breast Cancer. Five human and 15 animal studies identified in our searches point to a connection between alcohol intake and changes in important metabolic pathways that when altered may increase the risk of developing breast cancer. Alterations in blood hormone levels, especially elevated estrogen-related hormones, have been reported in humans. Several cell line studies suggest that the estrogen receptor pathways may be altered by ethanol. Increased estrogen levels may increase the risk of breast cancer through increases in cell proliferation and alterations in estrogen receptors. Human studies have also suggested a connection with prolactin and with biomarkers of oxidative stress. Of 15 animal studies, six reported increased mammary tumorigenesis (four administered a co-carcinogen and two did not). Other animal studies reported conversion of ethanol to acetaldehyde in mammary tissue as having a significant effect on the progression of tumor development. Fifteen cell line studies suggested the following mechanisms:

- increased hormonal receptor levels
- increased cell proliferation
- a direct stimulatory effect
- DNA adduct formation
- increase cyclic adenosine monophosphate (cAMP)
- change in potassium channels
- modulation of gene expression.

Colorectal Cancer. One human tissue study, 19 animal studies (of which 12 administered a co-carcinogen and seven did not), and 10 cell line studies indicate that ethanol and acetaldehyde may alter metabolic pathways and cell structures that increase the risk of developing colon cancer. Exposure of human colonic biopsies to acetaldehyde suggests that acetaldehyde disrupts epithelial tight junctions.

Among 19 animal studies the mechanisms considered included:

- mucosal damage after ethanol consumption
- increased degradation of folate
- stimulation of rectal carcinogenesis
- increased cell proliferation
- increased effect of carcinogens.

Ten cell line studies suggested:

- folate uptake modulation
- tumor necrosis factor modulation
- inflammation and cell death
- DNA adduct formation
- cell differentiation
- modulation of gene expression.

One study used a combination of animal and cell line and suggested intestinal cell proliferation and disruption of cellular signals as possible mechanisms.

Conclusions: Based on our systematic review of the literature, many potential mechanisms by which alcohol may influence the development of breast or colorectal cancers have been explored but the exact connection or connections remain unclear. The evidence points in several directions but the importance of any one mechanism is not apparent at this time.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/alccan/alccan.pdf.

Executive Summary

Alcohol Consumption and Cancer Risk: Understanding Possible Mechanisms for Breast and Colorectal Cancers

The purpose of our assessment of alcohol and cancer induction is to explore the possible underlying causal mechanism(s) of the association between alcohol consumption and breast and colorectal cancers. Therefore, we developed four Key Questions that address the potential mechanism(s) by which alcohol might be involved in the development of breast and colorectal cancers. The primary evidence base to address these questions consisted of experimental studies of humans, animals, and cell lines where alcohol exposure could be controlled. In addition to this evidence base we also considered epidemiology studies where alcohol exposure was not controlled (including those in patients with or without cancer) and hypothesis-generating studies that examined potential metabolic pathways connecting alcohol to cancer risk. These studies were considered in a separate evidence base that did not directly address the Key Questions.

Methods

The following Key Questions will be addressed in this report:

1. *What are the likely causal mechanisms by which alcohol contributes to the development of breast cancer? Which of the possible mechanisms (e.g., induction of P450 cytochromes and carcinogen metabolism, effects on blood hormone concentrations, effect of acetaldehyde or other alcohol metabolite on apoptosis and DNA repair, interactive effects on other nutritional factors, or others) are likely to be most important in breast cancer development?*
2. *For the most likely mechanisms of action involving alcohol and the development of breast cancer, how might other factors modify the effect of alcohol on breast cancer (for example, age, latency of effect, intensity, duration, and recency of exposure, presence of co-carcinogens, presence of threshold effect)? Do the causal mechanisms vary by cell type or other tumor characteristics?*
3. *What are the likely causal mechanisms by which alcohol contributes to the development of colorectal cancer? Which of the possible mechanisms (e.g., induction of P450 cytochromes and carcinogen metabolism, effects on blood hormone concentrations, effect of acetaldehyde or other alcohol metabolite on apoptosis and DNA repair, interactive effects on other nutritional factors, or others) are likely to be most important in colorectal cancer development?*
4. *For the most likely mechanisms of action involving alcohol and the development of colorectal cancer, how might other factors modify the effect of alcohol on colorectal cancer (for example, age, latency of effect, intensity, duration, and recency of exposure, presence of co-carcinogens, presence of threshold effect)? Do the causal mechanisms vary by cell type or other tumor characteristics?*

To address these Key Questions we searched electronic databases for information on ethanol consumption and the possible risks for breast and colorectal cancers. Thirty-five breast cancer studies (five in humans, 15 in animals, and 15 in cell lines) and 31 colorectal cancer studies (one in humans, 19 in animals, 10 in cell lines, and one combination [animal and cell lines]) were included in the report. Information on study design and conduct was used to judge individual study internal validity. Data on experimental model, mechanism(s) examined, amount and duration of ethanol exposure, cancer formation, and intermediate outcomes were abstracted and tabled for review and discussion.

Evidence for Alcohol Consumption and Cancer Risk: Understanding Possible Mechanisms for Breast and Colorectal Cancers

Breast Cancer Studies

Human studies. We included five studies to evaluate the possible mechanisms for alcohol consumption and breast cancer risk: the first study examined effects of alcohol on estradiol, estrone, estrone sulfate, testosterone, androstenedione, progesterone, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenediol; the second study examined the effects of alcohol on plasma and urinary hormone concentrations in premenopausal women; a third study examined the effect of alcohol on prolactin levels in menopausal women using estradiol replacement; a fourth study examined the effects of alcohol on estrogen levels in postmenopausal women; and a fifth study examined the relationship of alcohol consumption with antioxidant nutrients and biomarkers of oxidative stress. Although none of these five studies reported direct evidence of cancer, we included them given that alcohol was administered to assess possible hormonal mechanism(s) and biomarkers of oxidative stress.

Animal studies. We included 15 studies using animal models to evaluate the possible mechanisms for alcohol consumption and breast cancer risk. Outcomes measured varied across studies. Of the 15 included studies, 14 reported on the type of mechanism(s) examined and one did not. The type of mechanisms examined in the 14 studies included elevated levels of estrogen and or progesterone, biotransformation to acetaldehyde, formation of deoxyribonucleic acid (DNA) adducts, elevation of serum prolactin, suppression of cellular immunity, enhancement of rate of tumor progression, and effect on DNA synthesis. Administration and duration of ethanol exposure varied across all studies. Studies also varied on whether a carcinogen was administered to induce carcinogenesis. Of the 15 studies, 10 reported the use of a carcinogen to induce cancer:

- dimethylene (a) anthracene [DMBA] (five studies)
- N-methyl-N-nitrosurea [MNU] (two studies)
- N-nitrosodimethylamine [NMDA] and 4-methylnitrosoamino-1-3-pyridyl-1-butanone [NNK] (one study)
- MADB106 [one study]
- bittner virus [one study].

Cell line studies. We included 15 studies using cell lines to evaluate the possible mechanisms for alcohol consumption and breast cancer risk. Twelve studies administered ethanol alone, and two studies administered ethanol combined with acetaldehyde. Cell lines examined in the studies included:

- MCF-7 (six studies)

- MCF-10F (two studies)
- T4TD (one study)
- MM46 tumor cells (one study)
- MCF-7 + T47D (one study)
- MCF-7 + T84 (one study)
- MDA-MB-453 (one study)
- MCF-7 + T47D + MDA-MB-231 (one study)
- MCF-7 +ZR75.1 + BT-20 + MDA-MB-231 (one study).

Various mechanisms were reported by these studies: hormonal-related, DNA-adduct formation, inflammation and cell death, cell differentiation, increase cyclic adenosine monophosphate (cAMP), change in potassium channels, and modulation of gene expression.

Colorectal cancer studies.

Human study. We included one study using human tissues to evaluate the possible mechanism for alcohol consumption and colorectal cancer risk. The study exposed colonic mucosa to acetaldehyde vapor. Although the study did not report direct evidence to show causation of cancer, the authors concluded that acetaldehyde may cause an increase in risk of colon cancer via loss of cell-cell adhesion.

Animal studies. We included 19 studies using animal models to evaluate the possible mechanisms for alcohol consumption and colorectal cancer risk. Outcomes varied across all studies. Of the 19 included studies, 17 reported on the type of mechanism(s) examined and two did not. The type of mechanisms examined in the 17 studies included:

- cytochrome system expression
- generation of acetaldehyde
- DNA methylation
- effect of folate metabolism
- cell proliferation
- formation of acetaldehyde by human colonic bacteria
- local mucosal effect
- effect on various phases of carcinogenesis.

Administration and duration of ethanol exposure varied across all animal studies. Studies also varied on whether a carcinogen was administered to induce carcinogenesis. Of the 19 studies, 12 reported the use of a carcinogen to induce cancer:

- 1,1-dimethylhydrazine (DMH) (six studies)
- methylazoxymethanol (MAM) acetate (one study)
- acetoxymethyl-methylnitrosamine (AMMN) (one study)
- AMMN + cyanamide (CY) (one study)
- azoxymethane (AOM) (three studies).

Cell line studies. We included 10 studies using cell lines to evaluate the possible mechanisms for alcohol consumption and colorectal cancer risk. Cell lines examined in the studies included:

- Caco-2 (six studies)
- HT-29 (one study)
- colonic mucosa cells (one study)
- Caco-2 + HT-29 (one study)
- HT-29 + SW-1116 + HCT-15 (one study).

Various mechanisms were reported by these studies:

- folate uptake modulation
- tumor necrosis factor modulation
- inflammation and cell death
- formation of crosslinks with DNA
- cell differentiation
- modulation of gene expression.

Amount and duration of ethanol and/or acetaldehyde varied across all studies. Seven studies administered ethanol alone, while three studies administered ethanol combined with acetaldehyde.

Combination study (animal, cell line). We included one study that used a combination of animal (mice) and cell line (Caco-2) to evaluate the possible mechanisms for alcohol consumption and colorectal cancer risk. Intestinal cell proliferation as a result of phosphatidylethanol accumulation was the examined mechanism. The animal study administered ethanol, and the cell line study administered either ethanol or acetaldehyde. The primary outcome reported was disruption of cellular signals.

Discussion

The relationship between alcohol consumption and the risk of breast and colorectal cancers has been assessed in several systematic reviews and epidemiology studies (cohort and case-control studies). In this report, we looked at the potential mechanism(s) connecting both breast and colorectal cancers with alcohol consumption, under the assumption that there is a causal relationship. Our report did not focus on such a causal relationship reported in epidemiology literature where alcohol consumption was not under experimental control, but rather on potential mechanism(s) in studies that administered either alcohol or acetaldehyde in the absence of cancer. Only the human studies that actually administered ethanol regardless of experimental model were abstracted and included in the primary evidence base to assess possible mechanism(s). In addition, given that acetaldehyde is a metabolite of ethanol, we included animal studies that administered either alcohol and/or acetaldehyde in our evidence base. In humans, acetaldehyde levels in the blood are either very low or undetectable following alcohol consumption. Epidemiology studies that administered survey questionnaires to assess alcohol consumption and cancer risk and hypothesis-generating studies that examined potential pathways connecting alcohol to cancer risk were included as a separate evidence base.

The majority of the animal studies that chemically induced tumors through the administration of both alcohol and a carcinogen reported an increase in the carcinogenic effect; however, these studies can only offer indirect evidence of a connection between alcohol consumption and increased cancer risk in humans. Most of these studies varied in terms of quantity of ethanol and timing of administration relative to the carcinogen that was used in the study to induce carcinogenesis. Though some of the possible mechanisms identified in this report have been evaluated in a variety of experimental models (i.e., human, animals, cell lines), others have simply been examined as hypothesis generating and as such may call for future research.

Breast cancer. Both human and animal studies included in our primary evidence base point to a connection between alcohol intake and changes in blood hormone levels, especially elevated levels of estrogen and androgens in humans. Several cell line studies also suggest that estrogen receptor pathways may be altered by ethanol. Increased estrogen levels may increase the risk of breast cancer through increases in cell proliferation and alterations in estrogen receptors. Elevation in prolactin levels were also examined in human and animal studies. While not as extensive as the estrogen-related studies, these studies give some indication that alcohol consumption may alter prolactin levels and increase the risk of developing breast cancer. In order to report the role of oxidative stress in breast cancer, one human study measured changes in the levels of serum biomarkers.

The formation of acetaldehyde after ethanol consumption and its involvement in breast cancer has been examined in human epidemiology studies of enzyme polymorphism. Polymorphism in the enzymes that metabolize ethanol may increase an individual's exposure to toxic metabolites such as acetaldehyde and influence cancer risk if acetaldehyde is involved in breast cancer development. In animal studies, conversion of ethanol to acetaldehyde in mammary tissue has been reported to have a significant effect on the progression of tumor development. Events downstream from acetaldehyde are likely being altered by the presence of acetaldehyde and may lead to enhanced tumor development.

Enhancement of cell proliferation and tumor progression related to ethanol consumption and conversion to acetaldehyde were examined in animal and cell line studies. The findings of these studies suggest that alterations in cell proliferation due to alcohol exposure may be a possible mechanism increasing breast cancer risk.

Colorectal cancer. One human study reported that acetaldehyde disrupts epithelial tight junctions and cell adhesion. Several animal studies also looked at the effects of acetaldehyde in the colon and reported the following: mucosal damage after ethanol consumption, increased degradation of folate, stimulation of rectal carcinogenesis, and an increased effect of carcinogens in the presence of acetaldehyde. In cell line studies, acetaldehyde exposure was reported to influence the initial steps of colonic carcinogenesis and later tumor development and decrease the activity of some brush border enzymes. Finally, a study using human tissue, animal tissue, and a cell line found evidence that acetaldehyde stimulates cell proliferation in intestinal crypt cells and therefore acetaldehyde may act as a cocarcinogen in the colon. These studies (human, animal, and cell line) combine to suggest that acetaldehyde production in the colon may provide a potential causal mechanism by which alcohol contributes to the development of colon cancer.

An effect of ethanol consumption on cell proliferation in the colon was investigated in a combination study (animal and cell line). In this study, chronic alcohol exposure resulted in disruption of signals that normally restrict proliferation in highly confluent intestinal cells, thereby facilitating abnormal intestinal proliferation. Several animal studies reported enhanced growth of mucosal tissue after chronic ethanol consumption. Cell studies indicate that exposure to ethanol and acetaldehyde increases cell proliferation and damages DNA which may contribute to cancer development. Together these studies suggest that ethanol and acetaldehyde exposure in the colorectal mucosa may increase cell proliferation and be a potential mechanism connecting alcohol consumption to colorectal cancer risk.

Conclusions

Based on our systematic review of the literature, many potential mechanisms by which alcohol may influence the development of breast or colorectal cancers have been explored but the exact connection or connections remain unclear. The evidence points in several directions but the importance of any one mechanism is not apparent at this time. Several mechanisms have been proposed and human, animal, and cell line studies have provided evidence in support of several mechanisms, but the findings have been inconsistent. The diversity of experimental protocols among the studies included in this report could have contributed to the lack of consistency. Furthermore, variation across included studies for both the route of administration and amount of ethanol may have influenced results. Based on animal studies alone, researchers may be inclined to infer a causal link between alcohol and the risk of breast or colorectal cancers. In addition, although a majority of the epidemiology studies reported that alcohol increased the risk of both breast and colorectal cancers, we cannot discount uncontrolled confounding by diet and related lifestyles.

Evidence Report

Chapter 1. Introduction

Scope

The purpose of this report is to systematically and objectively synthesize evidence from the basic science literature to clarify the possible causal mechanisms by which alcohol may contribute to cancer risk, focusing on the induction and development of breast cancer and colorectal cancer under the assumption that there is a causal relationship. Therefore, the primary evidence base for this report consists of studies that administer ethanol or acetaldehyde to humans, animals, tissues, or cells and then look for the development of breast or colorectal cancer, or for changes in metabolic pathways and cellular structures that may increase the risk for developing these cancers. Case-control and other epidemiology studies are not included in the primary evidence base for assessment of possible mechanisms. However, such studies may provide insight into the dose/response relationship between alcohol consumption and cancer risk.

Apart from alcohol (i.e., ethanol) and water, the exact composition of most alcoholic beverages (e.g., beer, wine, or distilled spirits) on the market remains confidential proprietary information.[1] Therefore, the scope of this report is limited to ethanol. Other compounds (or contaminants) found in various alcoholic beverages that may play a role in the development of breast and colorectal cancers are outside the scope of this report. These compounds include nitrosamines, aflatoxins, polyphenols, ethyl carbamate (urethane), asbestos, and arsenic compounds.[1-4]

In addition, studies that evaluated tumor progression or metastatic spread of either breast or colorectal cancer during alcohol consumption are outside the scope of this report because they are not examining the mechanisms underlying the association of alcohol and the risk of developing cancer.

Ethanol Metabolism

Orally-ingested ethanol from an alcoholic drink is rapidly and almost completely absorbed by the stomach, small intestines, and colon. The bioavailability of ethanol, the fraction of the ingested dose that reaches the systemic circulation, is about 80%.[5] Therefore a large portion of ingested ethanol reaches the circulation (i.e., blood alcohol concentration) and is distributed to all body tissues including the breast, colon, and rectum. Blood alcohol concentration, however, may vary depending on the rate of gastric emptying and degree of metabolism during this first pass via the stomach and liver (i.e., first-pass metabolism of ethanol).[6-8]

Ethanol is metabolized in the body by two pathways (i.e., oxidative and nonoxidative).[8] However, the nonoxidative pathway is minimal compared to the oxidative pathway.[8] The liver is the major organ for the oxidative metabolism of ethanol.[9,10] Ethanol is converted into acetaldehyde by cytosolic alcohol dehydrogenase (ADH).[9-11] Due to variation in gene encoding there are multiple isoenzymes of ADH that vary in their enzyme activity (ADH1A, ADH1B*1, ADH1B*2, ADH1B*3, ADH1C*1, ADH1C*2, ADH4, ADH5, ADH6, and ADH7).[2,3,9,11-17] The ADH1B*2 is lower in frequency amongst Caucasians and higher among Asians and is about 40 times more active compared to the ADH1B*1 in the conversion of ethanol to acetaldehyde.[18] ADH1C*1 is very common in Asians, and metabolizes ethanol 2.5 times faster compared to ADH1C*2.[18,19] Among individuals who consume alcohol, ADH1C*1, a fast-acting metabolizer of ethanol, results in accumulation of acetaldehyde. As a result of increased levels of acetaldehyde, these individuals may experience uncomfortable side effects, and may well have a tendency to consume less alcohol.[18,19] The genetic polymorphism of ADH leads to differences in individual ethanol metabolism and individual differences in the susceptibility to alcohol-related tissue damage.[8,18]

Acetaldehyde, a metabolite of ethanol, is further metabolized to acetate primarily by mitochondrial aldehyde dehydrogenase (ALDH2).[9,11] ALDH2 accounts for the greater part of acetaldehyde breakdown and exists as ALDH2*1 and ALDH2*2. Individuals with ALDH2*2 have blood acetaldehyde levels 20 times higher compared to those with ALDH2*1.[18] Acetaldehyde is a highly toxic metabolite that binds to many cellular proteins and may be responsible for damage in the liver as well as other body tissues.[8] It binds to deoxyribonucleic acid (DNA), resulting in the formation of a DNA adduct which may influence cancer development.[3,11] Presence of a DNA adduct is a sign of exposure to specific cancer-causing agent, and is indicative of growing damage to the DNA.[3,11,13] Acetaldehyde is a cancer-causing agent in animals.[14]

During each oxidative process, nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH. In the liver, ethanol metabolism also involves microsomal cytochromes P450 2E1 (CYP2E1).[11] This pathway produces reactive oxygen species (ROS) such as superoxide anions and hydroxyl radicals which may increase the risk of tissue damage.[2,8,11]

Nonoxidative metabolism of alcohol involves two pathways.[8] One pathway results in the formation of fatty acid ethyl esters and the other the formation of phosphatidyl ethanol.[8,9]

ADH is present in the human colonic mucosa as well as in the microflora inhabiting the colon, and ethanol is metabolized to acetaldehyde by ADH in both of these locations.[20,21] ADH activity is significantly higher in the mucosa of the rectum than the colon.[21] Aldehyde dehydrogenase activity is much greater in the liver than in the colonic mucosa, which favors the accumulation of acetaldehyde in the colon.[20] Breast tissue contains ADH and CYP2E1.[10] Breast tissue converts ethanol to acetaldehyde which is then metabolized to acetate by xanthine oxidoreductase.

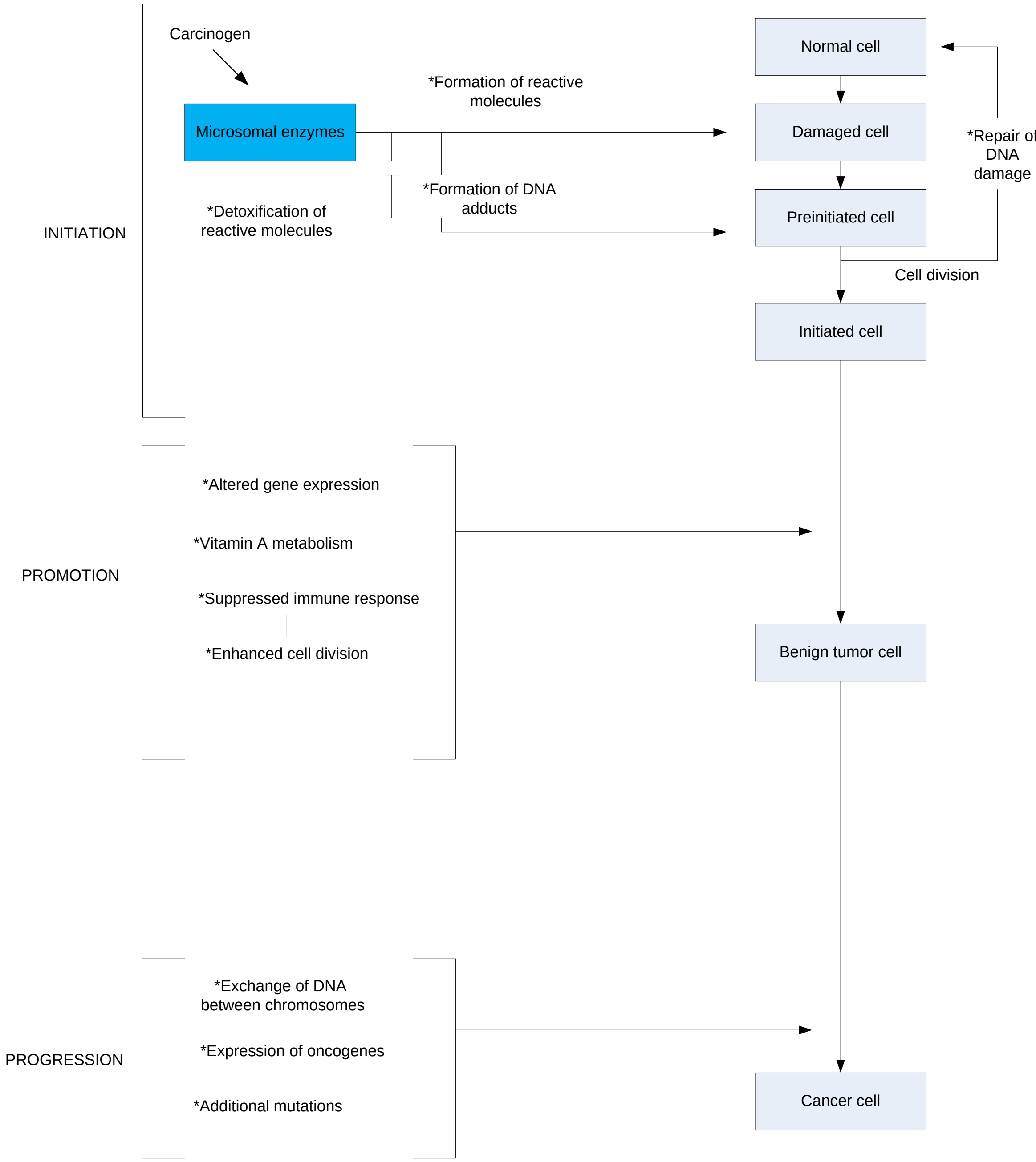
Alcohol and Cancer

Fewer than 10% of cancers can be attributed to an inherited genetic abnormality.[22] The majority of cancers are the result of changes in the gene structure due to the loss of control mechanisms that prevent cancer development.[22] Control mechanisms that may be altered during cancer development are: 1) tumor suppressor genes that lose their function causing a disruption in cellular adhesion and abnormal cell cycle progression, 2) DNA repair enzymes that become nonfunctional due to distorted methylation, and 3) proto-oncogenes that mutate into oncogenes.[22]

The course by which normal cells are transformed into cancer cells is termed carcinogenesis (see Figure 1).[3,14] When administered in combination with a recognized carcinogen, ethanol or its metabolite (acetaldehyde) produces reactive oxygen species (ROS).[10] ROS may increase the transformation of normal cells into cancerous cells in various organs by inhibition of DNA methylation as well as by interacting with metabolism of retinoids.[3,10,14,23,24] Alcohol and its metabolites have been implicated in all three stages of cancer formation (see the asterisks in Figure 1): [3,9,11,13,14,24,25]

- initiation stage by impact on DNA repair
- promotion stage by altered gene expression, enhanced cell division, suppression of immune response, and change in metabolism of vitamin A
- progression stage by expression of oncogenes, exchange of DNA between chromosomes, and additional mutations.

Figure 1. Three stages of carcinogenesis



*Source from http://www.niaaa.nih.gov/resources/graphicsgallery/immunesystem/lieb.htm[26]

Alcohol consumption is highly prevalent in the general U.S. population. The 2008 prevalence and trends data from the Behavioral Risk Factor Surveillance System indicate that about 54% of U.S. adults consumed alcohol within the past 30 days.[27] Though moderate alcohol consumption may have some potential health benefits, alcohol consumption has been identified as one of the major worldwide risks for burden of disease.[28] In the U.S., a standard drink is 12 fl oz (beer), 8 fl oz of malt liquor, 5 fl oz (wine), and 1.5 fl oz (80% proof distilled spirit).[29-32] Each is equivalent to 0.6 fluid ounces (12-14 g) of ethanol.[29-32] Moderate daily alcohol consumption in the U.S. for men is two drinks and for women is one drink.[29-32] However, variations have been reported worldwide in the definition of what is moderate for men and women.[29]

Several epidemiology studies have reported moderate to strong associations between the level of alcohol consumption and the incidence of cancers of the mouth, pharynx, larynx, esophagus, and liver.[2,24,33-35] Although the association between alcohol and breast and colorectal cancer is comparatively less strong than the association with these other cancers, given the high prevalence and incidence of breast and colorectal cancer, reducing the effect of any contributing factor may have a large overall impact on cancer incidence and prevalence.[3,24,33,34,36-41] Observed associations of alcohol consumption and cancer, however, can be confounded by other risk factors for cancer, such as age, smoking, family history, obesity and physical activity, race or ethnicity, and nutrition.[14,36,42-44] Because of the high prevalence of alcohol consumption, exploring the potential underlying mechanism(s) of the association between alcohol consumption and breast and colorectal cancers, if any, is essential in developing primary preventive measures. In view of the fact that alcohol consumption is a modifiable behavior,[45] recommending and promoting changes in behavior and appropriate preventive interventions may help reduce cancer risks in the general population.

Breast Cancer

According to the US National Cancer Institute (NCI), breast cancer is the most common cancer among women.[46] In 2009, it was anticipated that of the 192,370 women who were diagnosed, 40,170 would die of breast cancer.[46] Risk factors include family history, age at first birth, obesity in post menopausal women, dietary factors, alcohol consumption, early menarche, hormonal replacement therapy, low-dose irradiation, and lactation.[18,46] Estrogen-induced breast cancer may result from cell proliferation, activation of cytochrome P450, and DNA damage.[10] Cell proliferation is significant in the maintenance of normal and healthy breast tissue and these risk factors may alter cell proliferation in a direction that favors cancer development. Furthermore, enzyme polymorphism affects alcohol metabolism and could influence the effect of alcohol consumption on hormonal levels, thereby resulting in an increased risk of breast cancer.[47-50] Among patients diagnosed with breast cancer, unregulated breast epithelial cell growth has been reported.[51] Alcohol consumption has been investigated as a risk factor in the development of breast cancer. In a 2006 meta-analysis of 98 studies of alcohol and breast cancer, Key et al. reported that each additional 10 g ethanol/day resulted in a 10% increase in the odds ratio (OR) of risk of breast cancer associated with alcohol consumption.[52]

Colorectal Cancer

Of the estimated 75,590 men and 71,380 women diagnosed with colorectal cancer, 49,920 men and women were expected to die of the disease in 2009.[53] Among adults with cancer, colorectal cancer is the second most common cause of death.[54] Risk factors include:[13,14,53-58]

- age
- smoking
- low fiber diet
- high red meat/low fish intake
- inadequate intake of folate, B6 and retinoids
- obesity
- lack of physical activity
- low calcium intake
- alcohol (heavy consumption)
- an increase in colonic acetaldehyde level concentration
- chronic ulcerative colitis
- granulomatous colitis
- adenomatous polyps

In addition, following alcohol consumption, intracolonic ethanol is metabolized by colonic mucosal cells and intracolonic microbes. The risks of colorectal cancer development associated with alcohol consumption have been examined in epidemiology studies. In a 2004 meta-analysis of eight studies, Cho et al. reported that daily consumption of more than 45 g of alcohol increased the risk of colorectal cancer by 45%.[36] In addition, Homann et al. in a 2009 study reported that individuals with ADH1C1*1 homozygosity and consumption of more than 30 g of alcohol per day have significant increase risk of colorectal cancer.[19]

Chapter 2. Methods

Technical Expert Panel

ECRI Institute, in consultation with AHRQ, recruited a technical expert panel (TEP) to give input on key steps including the selection and refinement of the questions to be examined. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design and/or methodologic approaches do not necessarily represent the views of individual technical and content experts. The expert panel membership is provided in the front matter of this report.

ECRI Institute created a protocol for developing the evidence report. The process consisted of working with AHRQ and the TEP to outline the report's objectives and to finalize Key Questions for the review. These Key Questions are presented in the Scope and Key Questions section of the Introduction. Upon AHRQ approval, the draft protocol was posted on the AHRQ Web site at http://www.ahrq.gov/clinic/tp/alccantp.htm.

Peer Review and Public Commentary

A draft of the completed report was sent to the peer reviewers and the representatives of AHRQ. In response to the comments of the peer reviewers, revisions were made to the evidence report, and a summary of the comments and their disposition was submitted to AHRQ. Peer reviewer comments on a preliminary draft of this report were considered by the EPC in preparation of this final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

Key Questions

The purpose of our assessment of the basic science literature concerning alcohol and cancer induction is not to determine the extent to which alcohol is a risk factor for breast and colorectal cancers, but instead to explore the evidence suggesting possible underlying causal mechanism(s) of the association between alcohol consumption and breast and colorectal cancers (see broken arrows from alcohol to cancer induction in Figure 2 and Figure 3). Therefore, we developed four Key Questions that address the potential mechanism(s) by which alcohol might be involved in the development of breast and colorectal cancers.

Key Question 1. What are the likely causal mechanisms by which alcohol contributes to the development of breast cancer? Which of the possible mechanisms (e.g., induction of P450 cytochromes and carcinogen metabolism, effects on blood hormone concentrations, effect of acetaldehyde or other alcohol metabolite on apoptosis and DNA repair, interactive effects on other nutritional factors, or others) are likely to be most important in breast cancer development?

Key Question 2. For the most likely mechanisms of action involving alcohol and the development of breast cancer, how might other factors modify the effect of alcohol on breast cancer (for example, age, latency of effect, intensity, duration, and recency of exposure, presence of co-carcinogens, presence of threshold effect)? Do the causal mechanisms vary by cell type or other tumor characteristics?

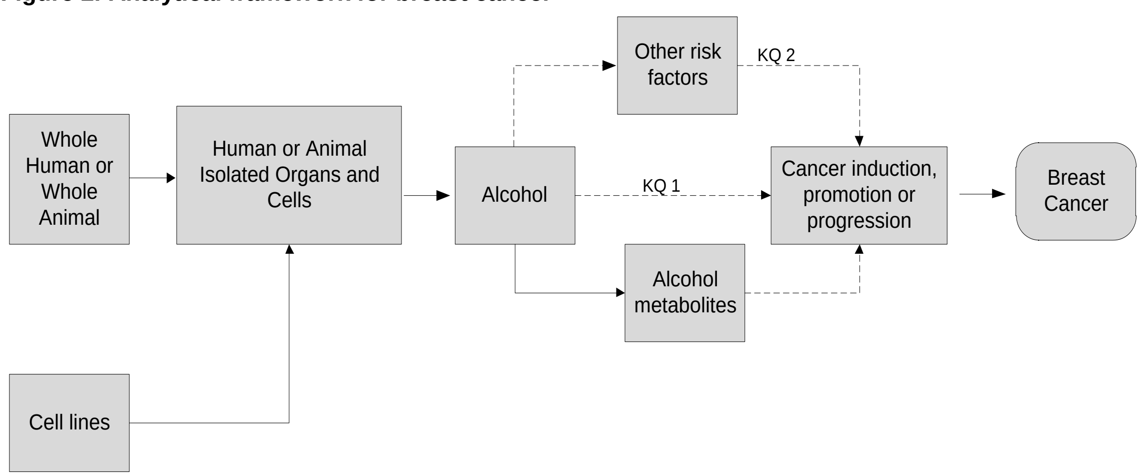
Key Question 3. What are the likely causal mechanisms by which alcohol contributes to the development of colorectal cancer? Which of the possible mechanisms (e.g., induction of P450 cytochromes and carcinogen metabolism, effects on blood hormone concentrations, effect of acetaldehyde or other alcohol metabolite on apoptosis and DNA repair, interactive effects on other nutritional factors, or others) are likely to be most important in colorectal cancer development?

Key Question 4. For the most likely mechanisms of action involving alcohol and the development of colorectal cancer, how might other factors modify the effect of alcohol on colorectal cancer (for example, age, latency of effect, intensity, duration, and recency of exposure, presence of co-carcinogens, presence of threshold effect)? Do the causal mechanisms vary by cell type or other tumor characteristics?

Analytical Framework

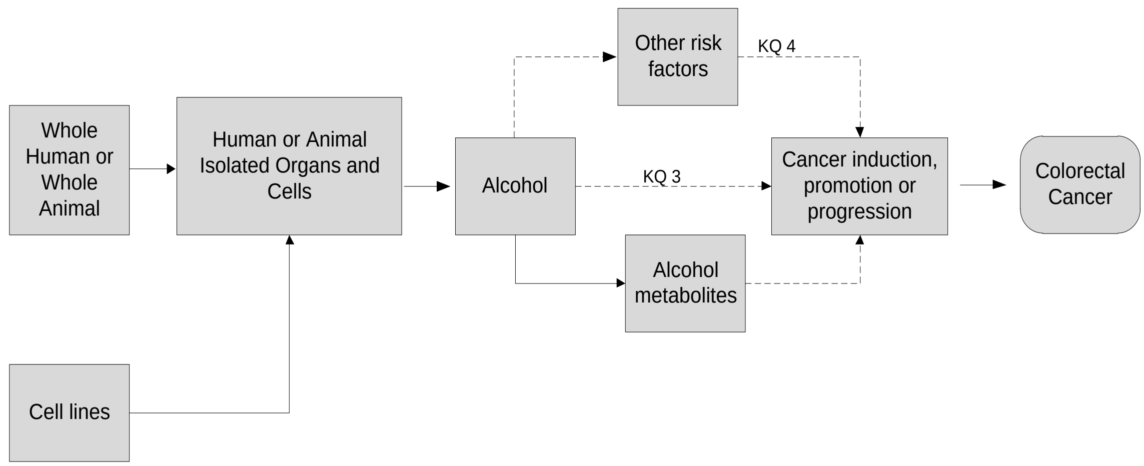
Figure 2 for breast and Figure 3 colorectal cancer portray analytical framework that visually describe the potential links in a chain of evidence that connect alcohol to breast and colorectal cancers. Contained within the framework are the Key Questions being addressed by this report and the potential areas of study (humans, animals, tissues, cells, ethanol and its metabolites) that can be manipulated to examine the assumed connection between alcohol consumption and an increased risk of developing breast or colorectal cancer.

Figure 2. Analytical framework for breast cancer



KQ: Key Question
KQ 1: effect of alcohol on stages of carcinogenesis
KQ 2: effect of alcohol and other risk factors on stages of carcinogenesis

Figure 3. Analytical framework for colorectal cancer



KQ: Key Question

KQ 3: effect of alcohol on stages of carcinogenesis
KQ 4: effect of alcohol and other risk factors on stages of carcinogenesis

Identification of Clinical Studies

The studies included in the primary evidence base for this technology assessment were identified using a multi-staged study selection process, and were based on inclusion criteria that were determined *a priori*, after the creation of the Key Questions and before any detailed examination of the literature base. Use of *a priori* inclusion criteria reduces the risk of bias because the decision to include or exclude each study is independent of the results of the study. In the first stage of the selection process, we performed a comprehensive literature search using broad criteria. In the second stage, we retrieved all articles that appeared to meet the *a priori* inclusion criteria, based on their published abstracts. In the final stage of the study selection, we reviewed the full text of each retrieved article, assessed its internal validity, and verified whether or not it met the *a priori* inclusion criteria.

Electronic Database Searches

We searched 11 external databases, including PubMed and EMBASE, for studies on possible mechanisms of alcohol and breast and colorectal cancer development (i.e., initiation, promotion, and progression) to identify evidence relevant to the Key Questions 1-4 using Medical Subject Headings and free text words. Additionally, we used some of the search terms and sources that were suggested by the Technical Expert Panel members on October 28, 2009. Two reviewers in the investigative team independently screened search results, selected studies to be included and reviewed each trial for inclusion. To supplement the electronic searches, we manually examined the bibliographies of included studies, scanned the content of new issues of selected journals, and reviewed relevant gray literature for potential additional articles. Gray literature includes reports and studies produced by local government agencies, private organizations, educational facilities, and corporations that do not appear in the peer-reviewed literature. Although we examined gray literature sources to identify relevant information, we only consider published, peer-reviewed literature in this report. During the peer review process, any new studies or data recommended were subjected to the same inclusion and exclusion criteria. A complete list of the databases searched and the search strategy used to identify relevant studies are presented in Appendix A.

Study Selection

Use of explicit inclusion criteria, decided upon before any data have been extracted from studies, is a vital tool in preventing reviewer biases. Some of the *a priori* criteria are based on study design, and other criteria ensure that the evidence is not derived from unusual patients or interventions, and/or outmoded technologies. We developed the same inclusion criteria for each Key Question that this report addresses.

Criteria for Inclusion/Exclusion of Studies in the Review

We used the following formal criteria to determine which studies were included in the primary evidence base that addresses each Key Question. These studies are primarily experimental studies where the exposure to ethanol or acetaldehyde could be controlled and precise biochemical measurements could be made.

1. Any study, regardless of design, that provides data on the possible causal mechanism(s) of any association between alcohol consumption and the development of breast and colorectal cancers in any population setting, including humans, animals, and in vitro experimental studies.
2. In order to assess the outcome measure of carcinogenesis, there must be no breast or colorectal cancer present in human and animal studies prior to the start of the study.
3. Cell lines should be appropriate to the study of breast and colorectal cancers in humans.
4. Studies that report on metastatic lesions or tumor invasion were excluded because they do not discuss the likely causal mechanism(s) of the tumor at the primary site (breast or colorectal).
5. When the same study was published more than once, we used the data from the most recent publication. However, if the older report had provided data that was not provided by the most recent report, we included such data.
6. Studies must have administered ethanol. Studies that administered alcoholic beverages such as beer or malt liquor were excluded given that the exact composition of such drinks remains confidential.

Studies that did not specifically control alcohol exposure were also considered in this report but were not included in the primary evidence base addressing the Key Questions. Hypothesis-generating studies examining metabolic pathways that may connect alcohol to cancer risk and epidemiology studies of alcohol exposure (including those in patients with or without cancer) were incorporated into the report in order to review and discuss this literature for comparison with our primary evidence base from experimental studies.

Literature Review Procedures

The abstracts for all identified documents were downloaded into the Mobius Analytics SRS 4.0 Web-based system for conducting systematic reviews. Using this system, we assessed abstracts in order to either include or exclude identified documents based on our inclusion criteria. If the abstract was missing or had insufficient information to make a decision on inclusion we ordered the full article. Full articles were then retrieved for review and categorization using Web-based forms. The Web-based system provided a structured framework to build and manage the numerous documents identified by our searches.

The review process underwent four levels:

- **Level 1** – Abstract Review
- **Level 2** – Full Document Review
- **Level 3** – Background Document Review
- **Level 4** – Evidence Base Document Review.

Each level has an electronic form for capturing data about each document identified in our searches (see Appendix B for sample data abstraction forms).

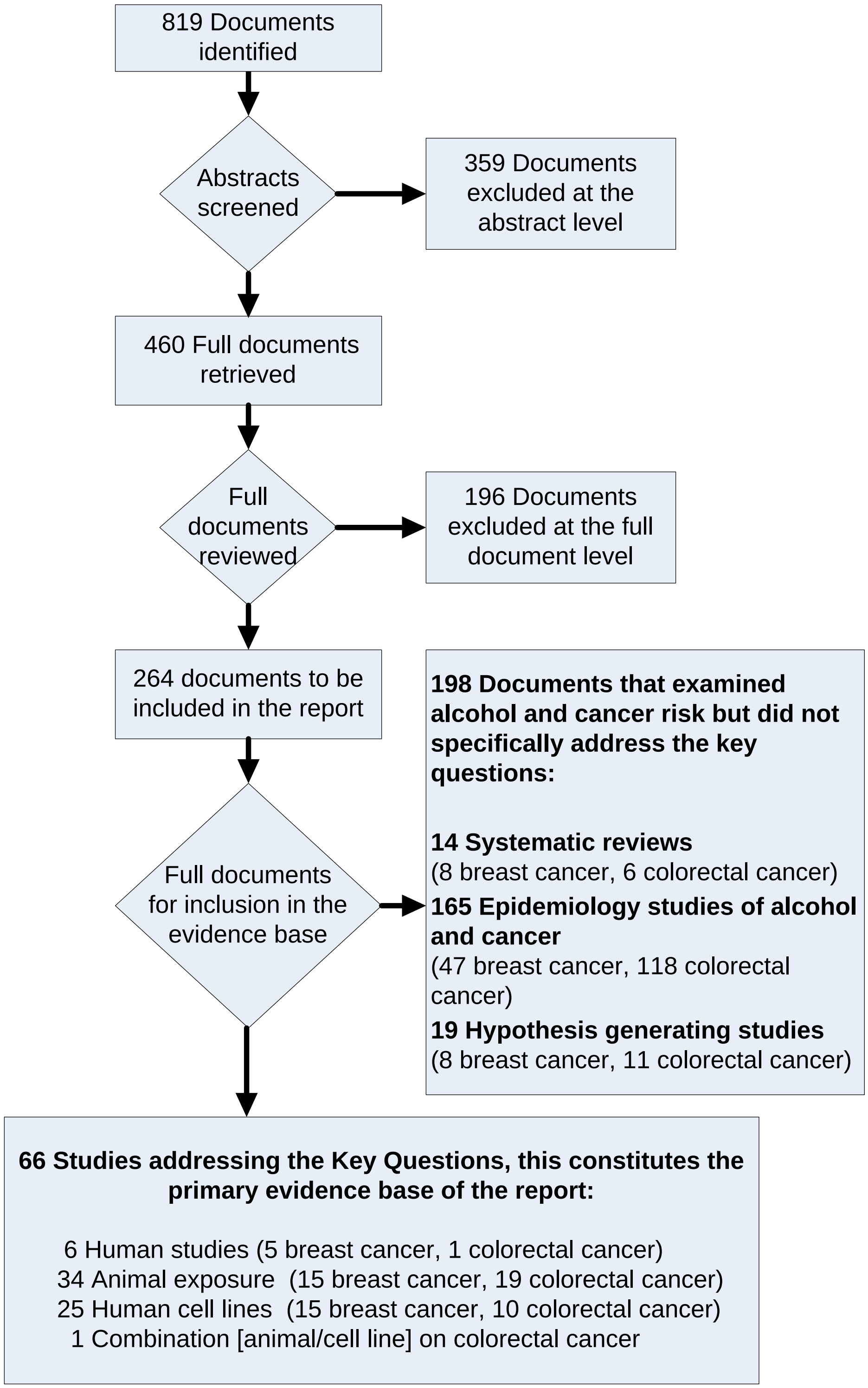
Data Abstraction and Data Management

All documents that were identified as belonging in the evidence base of the report underwent data abstraction using EXCEL spreadsheets. Table B-1 in Appendix B provides a list of the data abstracted from each study and placed in to a separate column in the spreadsheet. Some of the columns were modified depending on whether a study examined humans, animals, or cell lines. The information in the spreadsheets was later used to create the evidence tables in this report.

Disposition of the Documents Identified by Literature Searches

The SRS Web-based system allowed us to track all identified documents along with their complete citation. Literature searches were updated periodically and the new documents were added to the system and reviewed. Using the information contained in the SRS database we were able to create Figure 4 to illustrate an attrition diagram as well as separate tables that show the disposition of the documents identified by our literature searches. A total of 819 documents were identified by our searches. After review of the abstracts and then full documents, we included 264 documents for discussion within the report. Of these 264 documents, 66 met the requirements for the primary evidence base because they addressed one of the Key Questions. An additional 197 documents were included because they addressed issues related to alcohol and breast or colorectal cancer risk.

Figure 4. Disposition of the documents identified by literature searches



Assessing the Evidence for Each Key Question

Assessment of Internal and External Validity

A critical part in the process of creating a systematic review is assessing the validity of the results reported in each included study in the review. The validity of individual study results is determined in the context of the Key Questions these studies address. Internal validity is the extent to which a study's design and conduct are likely to have prevented bias and produced results that describe a true relationship.[59]

The members of the Technical Expert Panel proposed several methods for evaluating the internal validity of studies using animals, tissues, or cells as the primary experimental model.

- Evidence from experimental studies offer the most compelling evidence that a mechanism/pathway is directly involved in increasing cancer risk with alcohol intake.
- Use of alcohol concentration levels in animal studies that far exceed levels that occur in humans are considered of low applicability.
- Cell lines should be appropriate to the study of breast and colorectal cancer in humans.

To ultimately establish the presence of a contributory cause between alcohol consumption and breast or colorectal cancer, the following criteria have to be fulfilled: association, exposure prior to the association, and demonstration that changing the cause alters the effect.[14,60-63] Other supportive criteria such as strength of association, consistency of association, biological plausibility, and a dose-response relationship can be used to establish contributory cause.[60-63]

For this systematic review, we applied the "direct" vs. "indirect" evidence concept.[64] Direct assessment measures are those which provide *direct* evidence that alcohol causes either breast or colorectal cancer. Such evidence as shown in Figure 1 may confirm the steps during cancer formation and possible sites of action of alcohol thus demonstrating a contributory cause.

Indirect measures typically focus on predictors that are correlated to carcinogenesis, but do not measure actual causation. Some of the most common indirect assessment measures include:[3,10,13,14,18,41,55,65-81]

- increased androgen and estrogen concentration
- inactivation of the BRCA1 gene
- formation of new capillaries (angiogenesis)
- depletion of s-adenosylmethionine (SAM)
- low iron levels, low folate and vitamin B_{12} levels
- induction of epidermal growth factor
- increase in tumor necrosis factor-alpha receptor
- acetaldehyde formation by colonic bacteria
- induction of CYP2E1
- impairment of retinoic acid

- generation of reactive oxygen species and reactive nitrogen species
- immune suppression (effects on peripheral T- and B-lymphocytes)
- increase in cell membrane permeability
- interference with DNA repair (acetaldehyde-DNA adducts)
- increased levels of biomarkers of oxidative stress.

Because of the focus on the *how* and *why* of causation of cancer, indirect measures are critical in our efforts to improve the evidence of direct causation in ongoing and future research of possible causal mechanisms explaining the increased risk of breast and colorectal cancer with alcohol consumption.

For this report, experimental studies that show direct evidence were treated as stronger evidence than studies of association which only showed indirect evidence. The strength of evidence supporting each proposed mechanism relating alcohol intake to the development of breast or colorectal cancer were categorized as either "Sufficient" or "Insufficient." Three domains were evaluated: the potential risk of bias, or "internal validity" of the evidence base, the size of the evidence base (number of studies examining any one proposed mechanism), and the consistency of the findings (agreement across studies examining the same proposed mechanism).

External validity is the extent to which the findings and conclusions from a study or report can be translated to a specific setting or population (i.e., generalizability).[59] Generalizability is always strongest when results are collected in the specific setting or population of interest. However, clinical studies often cannot be conducted in such a setting or population, and results are instead collected from a more rigidly defined and less generalizable patient population. Human studies have more external validity than animal or cell line studies.

Data Synthesis

No meta-analyses were planned for this report. Given that this systematic review is hypothesis-summarizing and generating, we present a narrative summary of the findings based on the number of different mechanisms proposed and the studies showing support or lack of support for each mechanism.

Assessment of Internal Validity of Breast and Colorectal Studies

Internal validity, especially in the context of clinical studies, is the extent to which a study's design and conduct are likely to have prevented bias.[59,82] However, in the context of this report, which is assessing the results of human, animal and in vitro studies, we defined internal validity as the extent to which a direct relationship can be seen between the result of a given study and an increase in the risk of developing breast or colorectal cancer following ethanol consumption. Although we believe that the included studies are valid in design and outcomes measured for their intended purpose, we needed a measure of internal validity that was relevant to the connection between study results and cancer risk in humans. Therefore we considered human studies that administered alcohol having a higher internal validity than animal or in vitro studies. Animal studies that administered alcohol and did not use any known co-carcinogen were considered as having a higher internal validity (more direct relationship to an increase in cancer risk) than studies that administered a carcinogen. Studies that administered acetaldehyde or known carcinogens were considered as having lower internal validity and a less direct relationship with an increase in cancer risk in humans who consume alcohol.

Assessment of External Validity of Breast and Colorectal Studies

In our report we did not identify any studies using human subjects that directly assessed the possible mechanism(s) associated with risk of breast cancer following alcohol consumption. However, we did identify one human study that indirectly reported on colorectal cancer risk association with alcohol consumption: exposure of colonic biopsy tissues to acetaldehyde.[83] For the animal studies, generalizability may be compromised by administering ethanol concentrations that far exceed levels suitable for human consumption, by administering acetaldehyde, and by co-administering a known carcinogen.[73,82,84] Therefore, the results of these studies may not be directly applicable to human settings.

Chapter 3. Results

Evidence Base Describing Possible Mechanisms Connecting Alcohol Consumption and Breast Cancer Risk

Human Studies

We included five studies (see Table C-1 in Appendix C) that evaluated the possible mechanisms connecting alcohol consumption and breast cancer risk: the first study examined effects of alcohol on estradiol, estrone, estrone sulfate, testosterone, androstenedione, progesterone, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenediol;[85] the second study[86] examined the effects of alcohol on plasma and urinary hormone concentrations in premenopausal women; the third study[87] examined the effect of alcohol on prolactin levels in menopausal women using estradiol replacement; the fourth study[88] examined the effects of alcohol on estrogen levels in postmenopausal women; and the fifth study[76] examined the relationship of alcohol consumption with antioxidant nutrients and a biomarker of oxidative stress. Although none of these five studies reported direct evidence of cancer, we included them because alcohol was administered to examine alterations in hormonal mechanism(s) and biomarkers of oxidative stress that have been suggested to be linked to the development of breast cancer. Four studies[87-90] reported increased serum hormonal levels and one study[76] reported an increase in isoprostane levels, a biomarker of oxidative stress. Table C-1 in Appendix C provides a summary of study design, mechanisms examined, amount and duration of ethanol or acetaldehyde exposure, study results, and authors' conclusions.

In the study by Dorgan et al., 51 healthy postmenopausal women consumed 15 or 30 grams of alcohol per day or an alcohol-free placebo beverage through three 8-week dietary periods. Each dietary period was preceded by a 2- to 5-week washout period when participants did not consume any alcohol. The results showed an increase in serum levels of both estrone sulfate and DHEAS. While this study did not report any direct evidence to show causation of cancer, Dorgan et al. concluded that results suggest a possible mechanism by which consumption of one or two alcoholic drinks per day by postmenopausal women could increase their risk of breast cancer.[85] In the second study Reichman et al. examined 34 premenopausal women who consumed 30 g of ethanol daily for three menstrual cycles and no alcohol during three other cycles.[86] The results showed an increase in plasma DHEA sulfate, plasma estrone, plasma estradiol, and urinary estradiol. Reichman et al. concluded that these results suggest a possible mechanism between alcohol consumption and risk of breast cancer again because of changes in hormone levels.[86] In the third study, Ginsburg et al.[87] conducted two randomized, crossover studies in post menopausal women: study 1 administered ethanol (1 mL/kg, 95% ethanol) vs. isocaloric drink; study 2 was similar to study 1 except authors removed transdermal estradiol patches after administration of either ethanol or isocaloric drink. In both crossover studies, Ginsburg et al.[87] reported an increase in serum prolactin levels. In the fourth study Ginsburg et al.[88] administered ethanol (pineapple juice and 40% ethanol at a dose of 2.2 mL/kg of body weight [0.7 g/kg of body weight] in a total volume of 300 mL) vs. placebo to 24 postmenopausal women and reported a 3-fold increase in circulating estradiol levels in women on estrogen replacement therapy (ERT). In the fifth study Hartman et al.[76] administered a controlled diet plus each of three treatments (15 or 30 g alcohol/day or no-alcohol placebo beverage) to 53 postmenopausal women, during three 8-week periods in random order and reported that moderate alcohol consumption increased isoprostane, a biomarker of oxidative stress by 4.9%.

Animal Studies

We included 15 studies using animal models to evaluate possible mechanisms connecting alcohol consumption with breast cancer risk (see Table C-2 in Appendix C). Of the 15 included studies, 14 reported on the mechanism(s) and one[91] did not. The mechanisms examined in the 14 studies were:

- elevated levels of estrogen and or progesterone[92-94]
- biotransformation to acetaldehyde[95]
- formation of DNA adducts[96]
- elevation of serum prolactin[97,98]
- suppression of cellular immunity[99]
- enhancement of rate of tumor progression[100-103]
- effect on DNA synthesis[104,105]

Administration and duration of ethanol exposure varied across studies. Studies also varied on whether a carcinogen was co-administered to induce carcinogenesis. Of the 15 studies, 10 reported the use of a known carcinogen to induce cancer:

- dimethylene (a) anthracene [DMBA] (five studies)
- N-methyl-N-nitrosurea [MNU] (two studies)
- N-nitrosodimethylamine [NMDA] and 4-methylnitrosoamino-1-3-pyridyl-1-butanone [NNK] (one study)
- MADB106 [one study]
- bittner virus [one study].

Table C-2 in Appendix C provides a summary of mechanisms examined, amount and duration of ethanol or acetaldehyde exposure, carcinogen use, study results, and authors' conclusions.

Outcomes measured varied across studies. Overall, six studies reported increased cancer formation (four studies co-administered a carcinogen[92,93,103] and two studies did not[91,97]). The reported results of intermediate outcomes included:

- biotransformation of ethanol to acetaldehyde[95]
- increase in the formation of DNA adducts[96]
- increase in terminal-end bud density and a decrease in alveolar bud structures[94,104,105]
- a reduction in blood natural killer cytotoxicity[99]

Three studies reported no changes in outcomes and concluded that their findings did not support a link between alcohol consumption and the risk of breast cancer.[100-102]

Cell Line Studies

We included 15 studies using cell lines to evaluate possible mechanisms connecting alcohol consumption with breast cancer risk (see Table C-3 in Appendix C). Cell lines examined in the studies included:

- MCF-7 (six studies)
- MCF-10F (two studies)
- T4TD (one study)
- MM46 tumor cells (one study)
- MDA-MB-453 (one study)
- MCF-7 + T47D (one study)
- MCF-7 + T84 (one study)
- MCF-7 + T47D + MDA-MB-231 (one study)
- MCF-7 + ZR75.1 + BT-20 + MDA-MB-231 (one study).

Various types of mechanism were reported by these studies:

- hormonal-related[65,67-69,106]
- DNA adduct formation[107,108]
- effect on cell proliferation[51,109,110]
- increase cAMP[111]
- change in potassium channels[112]
- mammary gland mucin upregulation[113]
- smooth muscle up-regulation during transcription[114]

Amount and duration of ethanol and/or acetaldehyde exposure varied across all studies. Ten studies administered ethanol alone, and two studies administered ethanol combined with acetaldehyde. Table C-3 in Appendix C provides a summary of mechanisms examined, amount and duration of ethanol or acetaldehyde exposure, study results, and authors' conclusions.

Five studies reported an increase in the expression of mRNA,[68,106,113,115] two studies reported an increase in the formation of DNA adducts,[107,108] two studies reported an increase in cell proliferation,[65,69] two studies reported enhancement of ^{3}H-thymidine uptake,[51,110] one study reported up-regulation of smooth muscle myosin alkali light chain,[114] and one study[109] reported reduction in the expression ribosomal protein L7a.

Evidence Base for Describing Possible Mechanisms Connecting Alcohol Consumption and Colorectal Cancer Risk

Human Studies

We included one study (see Table C-4 in Appendix C) using human tissues to evaluate the possible mechanism connecting alcohol consumption with colorectal cancer risk. The study exposed colonic mucosa to acetaldehyde vapor.[83] Although no direct evidence to show a connection between acetaldehyde exposure and cancer risk was reported, the authors concluded that acetaldehyde may cause an increase in risk of colon cancer via loss of cell-cell adhesion.[83] Table C-4 in Appendix C provides a summary of study design, mechanisms examined, amount and duration of acetaldehyde exposure, study results, and authors' conclusions.

Animal Studies

We included 19 studies using animal models to evaluate the possible mechanisms for alcohol consumption and colorectal cancer risk (see Table C-5 in Appendix C). Of the 19 included studies, 17 reported on the mechanism(s) examined and two[116,117] did not. The mechanisms examined in the 17 studies included:

- cytochrome system expression[118,119]
- generation of acetaldehyde[70,120-123]
- DNA methylation[124]
- cell proliferation[125-127]
- local mucosal effect[128,129]
- effect on various phases of carcinogenesis[73,130,131]

Administration and duration of ethanol exposure varied across all studies. Studies also varied on whether a carcinogen was co-administered. Of the 19 studies, 12 reported the use of a known carcinogen to induce cancer:

- 1,1-dimethylhydrazine (DMH) (six studies)
- methylazoxymethanol (MAM) acetate (one study)
- acetoxymethyl-methylnitrosamine (AMMN) (one study)
- AMMN + cyanamide (CY) (one study)
- azoxymethane (AOM) (three studies).

Table C-5 in Appendix C provides a summary of mechanisms examined, amount and duration of ethanol or acetaldehyde exposure, carcinogen use, study results, and authors' conclusions.

Outcomes measured varied across studies. Among the studies that co-administered a carcinogen, six[73,123,126,128,129,132] reported increased cancer formation, one[131] reported suppression of cancer formation, and two reported no effect.[116,117] Another study that did not co-administer a carcinogen reported an increase in cancer formation.[121] The reported results of intermediate outcomes include:

- increase in the number of aberrant crypt foci[118,122,125,127]
- increase in microsomal ethanol-oxidizing system activity[120]
- increase in acetaldehyde level resulting in folate degradation[70]
- undermethylation of DNA[124]
- increase in the expression of CYP2E1[119]
- decrease in the formation of DNA adducts[130]

Cell Line Studies

We included 10 studies using cell lines to evaluate possible mechanisms connecting alcohol consumption with colorectal cancer risk (see Table C-6 in Appendix C). Cell lines examined in the studies included:

- Caco-2 (six studies)
- HT-29 (one study)
- colonic mucosa cells (one study)
- Caco-2 + HT-29 (one study)
- HT-29 + SW-1116 + HCT-15 (one study).

Various mechanisms were reported by these studies:

- folate uptake modulation[133]
- tumor necrosis factor modulation[75,133]
- inflammation and cell death[134]
- formation of crosslinks with DNA[135]
- initiation of cancer[136,137]
- cell differentiation[138]
- modulation of gene expression[139]

Amount and duration of ethanol and/or acetaldehyde varied across all studies (seven studies administered ethanol alone, three studies administered ethanol combined with acetaldehyde). Table C-6 in Appendix C provides a summary of mechanisms examined, amount and duration of ethanol or acetaldehyde exposure, study results, and authors' conclusions.

Outcomes varied across all studies. Reported results included:

- inhibitory effect on both 3H-folic and 3H-methotrexate uptake[140]
- increase in tumor necrosis factor-alpha receptor-1[75]
- inflammation resulting in increased phosphatidylserine production[134]
- increase in mRNA expression[74]

- dual effect on cell proliferation (acute acetaldehyde exposure inhibitory and chronic acetaldehyde exposure stimulating)[136]
- increase in sucrase and maltase activity[137,138]
- increase in alkaline phosphatase and sucrose activities, limited cytotoxicity[133]
- damage to DNA strands[135]
- lack of effect on the expression of HLA class 1 antigens[139]

Combination Study (Animal, Cell Line)

We included one study[141] that used a combination of animal (mice) and cell line (Caco-2) to evaluate the possible mechanisms connecting alcohol consumption with colorectal cancer risk (see Table C-7 in Appendix C). Intestinal cell proliferation as a result of phosphatidylethanol accumulation was the examined mechanism. The animal study administered ethanol and the cell line study administered either ethanol or acetaldehyde. Outcome reported was disruption of cellular signals. Chronic alcohol exposure resulted in an increase of maximal intestinal density.[141]

Systematic Reviews and Narrative Reviews of Epidemiology Studies

We identified and summarized the reported results and conclusions from 13 systematic reviews of epidemiology studies looking for an association between alcohol intake and cancer risk (seven on breast cancer [see Table 1], six on colorectal cancer [see Table 2]). While these studies were not considered part of our primary evidence base addressing the key questions of this report, they do provide important evidence connecting alcohol intake with breast and colorectal cancer risk in humans and provide a context for discussing the findings of the studies included in our primary evidence base. The tables provide the review objectives, the resources searched, inclusion criteria, a summary of results, and the authors' conclusions. Key areas examined by the systematic reviews of breast cancer included:

- alterations in estrogen-dependent pathways
- polymorphisms in one-carbon metabolism pathways
- interaction with dietary folate intake
- dose-response relationships between alcohol intake and cancer risk.

Key areas examined by the systematic reviews of colorectal cancer include differences in Japanese versus western populations, and amount of alcohol intake and cancer risk.

Table 1. Systematic reviews/meta-analyses for breast cancer epidemiology studies

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Suzuki et al. 2008[142]	To quantitatively assess the accumulated evidence on the association between alcohol intake and the risk of estrogen receptor (ER) and progesterone receptor (PR)– defined breast cancer subtypes and to evaluate whether the observed association differs across ER/PR status.	Eligible studies were identified by searching the MEDLINE database from January 1, 1970 through April 20, 2007 for relevant epidemiology studies of alcohol consumption in relation to the risk of breast cancer defined by ER/PR without any language restriction. <u>Evidence base</u>: Nineteen studies (4 prospective cohort studies and 16 case-control studies)	The risk of developing breast cancer was statistically significant comparing the highest vs. lowest consumption categories for developing: ER+ tumors 27% (1.17-1.38), all ER- tumors 14% (1.03-1.26), ER+PR+ tumors 22% (1.11-1.34), ER+PR- tumors 28% (1.07-1.53), but not ER-PR- tumors. An increase in alcohol consumption of 10 g of ethanol per day was associated with statistically significant increased risks for: all ER+ 12% (8%-15%), all ER- 7% (0%-14%), ER+PR+ 11% (7%-14%) and ER+PR- 15% (2%-30%), but not ER-PR-.	Estrogen-dependent pathway alone cannot account for the detected positive associations with alcohol for ER+PR+ and ER-PR+ tumors.
Lissowska et al. 2007[143]	To examine the role of genetic polymorphisms in the one-carbon metabolism pathway and breast cancer risk.	Epidemiology studies of methylenetetrahydrofolate gene (MTHFR A222V and E429A) polymorphisms and breast cancer risk published through August 2006 were identified through a PubMed search.	There was no significant association of breast cancer risk with nutrients involved in one carbon metabolism (i.e., folate, vitamins B2, B6, B12, methionine) or with alcohol intake.	Study did not support association between polymorphisms in the one-carbon metabolism pathway and the risk of breast cancer.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Lewis et al. 2006[144]	To summarize the available evidence from observational studies on this issue and a meta-analysis of the association between a common polymorphism in the 5,10-methylenetetra-hydrofolate reductase (MTHFR) gene.	MEDLINE and ISI Web of knowledge databases for relevant studies that were published through May 31, 2006. Evidence base: 19 studies (13 case-control studies and 9 cohort studies) of which seven cohort studies and one case-control study examined the interaction between alcohol and folate intakes with respect to risk of breast cancer.	Only two studies used the same cut off points for alcohol intake. Therefore, evidence for interaction between alcohol and folate intakes with respect to risk of breast cancer was inconclusive.	There is no association between a lack of dietary folate intake and breast cancer risk.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Key et al. 2006[52]	To give an up-to-date assessment of the association of alcohol with female breast cancer, addressing methodological issues and shortfalls in previous overviews.	MEDLINE, EMBASE, Pascal (BIDS), Science Citation Index (BIDS), Social Sciences Citation Index (BIDS), Index to Scientific and Technical Proceedings (via BIDS), Biological Abstracts (BIOSIS), Biological Sciences, AIDS and Cancer Research Abstracts, Biology Digest, Conference Papers Index, Cochrane Library, NHS National Research Register (NRR), SIGLE (System for Information on Grey Literature), NTIS (National Technical Information Service), TOXLINE. Evidence base: 98 studies (75,728 drinkers vs. 60,653 non-drinkers)	Excess risk associated with alcohol consumption was 22% (9%-37%). Each additional 10 g ethanol per day increases breast cancer risk by 10% (5%-15%). Estimated population attributable risk in the U.S.A. and U.K. were, 1.6% and 6.0%, respectively.	Association between alcohol and breast cancer may be causal.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Hamajima et al. 2002[34]	A collaborative reanalysis of individual data from 53 epidemiology studies, including 58,515 women with breast cancer and 95,067 women without the disease.	Resources searched were not reported by study authors. Evidence base: 53 studies (51 published, 2 unpublished)	The average consumption of alcohol reported by controls from developed countries was 6.0 g per day, i.e., about half a unit/drink of alcohol per day; greater in ever-smokers than never-smokers, (8.4 g per day and 5.0 g per day, respectively). Compared with women who reported no alcohol, relative risk (RR) of breast cancer was 1.32 (1.19-1.45, *p <0.00001*) for an intake of 35-44 g per day alcohol, and 1.46 (1.33-1.61, *p <0.00001*) for ≥45 g per day alcohol. For each additional 10 g per day intake of alcohol, the relative risk of breast cancer increased by 7.1% (5.5%-8.7%, *p <0.00001*).	Caution is needed to interpret the effect of alcohol on risk of breast cancer.
Corrao et al. 1999[145]	To compare the strength of the evidence provided by the epidemiology literature on the association between alcohol consumption and the risk of six cancers (oral cavity, esophagus, colorectum, liver, larynx, breast).	MEDLINE from 1966 up to and including 1998, articles reported by other bibliographic databases available at the University of Miami (*Current Contents* from 1996, EMBASE from 1980, CAB abstracts from 1973, and *Core Biomedical Collection* from 1993). Evidence base: 200 epidemiology studies (29 breast).	RR for dose of alcohol intake for breast cancer in the Mediterranean region* were: 1.6 (1.6-1.7) for 25 g per day, 2.7 (2.4-2.9) for 50 g per day, and 7.1 (5.8-18.6) for 100 g per day. RR for dose of alcohol intake in other areas* were: 1.2 (1.1-1.3) for 25 g per day, 1.5 (1.2-1.8) for 50 g per day, and 2.1 (1.4-3.1) for 100 g per day. **strata by region*	Based on weak dose-response relationship, there is need for well-conducted epidemiology studies.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Smith-Warner et al. 1998[39]	To assess the risk of invasive breast cancer associated with total and beverage-specific alcohol consumption and to evaluate whether dietary and nondietary factors modify the association.	Resources searched were not reported by study authors. Evidence base: 6 prospective studies that had at least 200 incident breast cancer cases, assessed long-term intake of food and nutrients, and used a validated diet assessment instrument.	For alcohol intake less than 60 g per day breast cancer risk increased linearly with increasing intake. Pooled multivariate RR for an increment of 10 g per day of alcohol (about 0.75-1 drink) was 1.09 (1.04-1.13). Multivariate-adjusted RR for total alcohol intake of 30 to <60 g per day (about 2-5 drinks) vs. nondrinkers was 1.41 (1.18-1.69). Limited data suggested that alcohol intake of at least 60 g per day were not associated with further increased risk. The specific type of alcoholic beverage did not strongly influence risk estimates. The association between alcohol intake and breast cancer was not modified by other factors.	Alcohol consumption is associated with a linear increase in breast cancer incidence in women over the range of consumption reported by most women. Among women who consume alcohol regularly, reducing alcohol consumption is a potential means to reduce breast cancer risk.
Longnecker 1993[146]	To evaluate the association between alcohol consumption and risk of breast cancer.	MEDLINE from 1996 through September 1992, all abstracts presented at the society for Epidemiology Research from 1989-1994. Evidence base: 38 epidemiology studies	RR of breast cancer following daily alcohol consumption were 1.11 (1.07-1.16) for one drink, 1.24 (1.15-1.34) for two drinks, and 1.38 (1.23-1.55) for three drinks.	Causal role of alcohol remains uncertain.

Table 2. Systematic reviews/meta-analyses for colorectal cancer epidemiology studies

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Mizoue et al. 2008[147]	To examine the association between alcohol consumption and colorectal cancer in Japanese.	Population-based cohort studies that were conducted in Japan, started between the mid-1980s and the mid-1990s, included more than 30,000 participants, obtained information on diet, including alcohol intake, using a validated questionnaire or a similar one at baseline, and collected incidence data for colorectal cancer during the follow-up period. Evidence base (5 cohort studies): • The Japan Public Health Center-based Prospective Study (JPHC) • The Japan Collaborative Cohort Study (JACC) • The Miyagi Cohort Study • The Takayama Study ○ According to the authors, the JPHC was treated as two independent studies (JPHC I and JPHC II) because of a difference in the dietary questionnaires used; thus, data from a total of five studies were analyzed.	In men, multivariate-adjusted pooled hazard ratios for alcohol intake of 23-45.9 g per day, 46-68.9 g per day, 69-91.9 g per day, and >92 g per day, compared with nondrinkers, were 1.42 (1.21-1.66), 1.95 (1.53-2.49), 2.15 (1.74-2.64), and 2.96 (2.27-3.86), respectively (*p* for trend <0.001). The association was evident for both the colon and the rectum. A significant positive association was also observed in women. Twenty-five percent of colorectal cancer cases were attributable to an alcohol consumption of >23 g per day.	When compared to Western populations, alcohol-colorectal cancer association seems to be more evident in Japanese.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Moskal et al. 2007[148]	To examine if current alcohol intake is associated with risk of colon and rectal cancer by summarizing the results of published prospective cohort studies with meta-analytic techniques.	Prospective cohort studies in MEDLINE published in English between 1990 and June 2005; (iii) referenced in MEDLINE. Since studies on specific types of alcohol (beer, wine, and liquor) were limited, the authors restricted the meta-analyses to total alcohol consumption on colorectal cancer risk. Studies in particular populations (i.e., cohorts of alcoholics or brewery workers) were not included. Evidence base: Sixteen prospective cohort studies	High alcohol intake was significantly associated with increased risk of colon 1.50 (1.25-1.79) and rectal cancer 1.63 (1.35-1.97). This was comparable to a 15% increase of risk of colon or rectal cancer for an increase of 100 g of alcohol intake per week. The association did not change significantly by anatomical site (colon, rectum).	Lifestyle recommendations for prevention of colorectal cancer should consider limiting alcohol intake.
Mizoue et al. 2006[149]	To review epidemiology findings regarding the association between alcohol drinking and colorectal cancer among the Japanese population.	MEDLINE from 1965 to 2005 Inclusion criteria: Epidemiology studies on the association between alcohol drinking and colorectal cancer incidence or mortality among Japanese. Evidence base: Eighteen studies (5 cohort studies and 13 case-control studies).	A moderate or strong positive association was observed between alcohol drinking and colon cancer risk in all large-scale cohort studies, with some showing a dose-response relationship, and among several case-control studies. A positive association with rectal cancer was also reported, but it was less consistent, and the magnitude of the association was generally weaker compared with colon cancer. The RR of colon or colorectal cancer increased even among moderate drinkers consuming <46 g of alcohol per day, levels at which no material increase in the risk was observed in a pooled analysis of Western studies.	Among the Japanese population, alcohol consumption perhaps may increase the risk of colorectal cancer. Association with colon cancer is probable, and that for rectal cancer is possible.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Cho et al. 2004[36]	To examine the relationship of total alcohol intake and intake from specific beverages to the incidence of colorectal cancer and to evaluate whether other potential risk factors modify the association.	The authors reported a pooled analysis of primary data from 8 cohort studies in 5 countries.	Increased risk for colorectal cancer was limited to persons with an alcohol intake of 30 g/day or greater (approximately >2 drinks per day), a consumption level reported by 4% of women and 13% of men. Compared with nondrinkers, the pooled RR were 1.16 (0.99-1.36) for persons who consumed 30 to <45 g per day and 1.41 (1.16-1.72) for those who consumed ≥45 g per day (p for trend <0.001). Evident for cancers of the proximal colon, distal colon, and rectum. No clear difference in relative risks was found among specific alcoholic beverage.	There was a correlation between a single determination of alcohol consumption and a modest relative elevation in the rate of colorectal cancer, mostly at the highest levels of consumption.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Corrao et al. 1999[145]	To compare the strength of the evidence provided by the epidemiology literature on the association between alcohol consumption and the risk of six cancers (oral cavity, esophagus, colorectum, liver, larynx, breast).	MEDLINE from 1966 up to and including 1998, articles reported by other bibliographic databases available at the University of Miami (*Current Contents* from 1996, EMBASE from 1980, CAB abstracts from 1973, and *Core Biomedical Collection* from 1993). Evidence base: 200 epidemiology studies (16 colon [12 case-control, 4 cohort], 14 rectum [11 case-control, 3 cohort]).	Colon studies** RR for dose of alcohol intake in colon studies (case-control) were 1.0 (1.0-1.1) for 25 g per day, 1.1 (1.0-1.2) for 50 g per day, and 1.1 (1.0-1.3) for 100 g per day. RR for dose alcohol intake in colon studies (cohort studies) were 1.4 (1.1-1.7) for 25 g per day, 1.9 (1.3-2.9) for 50 g per day, and 3.6 (1.6-8.5) for 100 g per day. ***Reported results were stratified by study design* Rectum studies*** RR for dose of alcohol intake in rectum studies among men were 1.1 (1.0-1.2) for 25 g per day, 1.2 (1.1-1.5) for 50 g per day, and 1.5 (1.2-2.2) for 100 g per day. RR for dose of alcohol in rectum studies among women were 2.3 (1.3-4.0) for 25 g per day, 5.0 (1.6-16.4) for 50 g per day, and 25.7 (2.5-267.6) for 100 g per day. ****Reported results were stratified by gender*	Based on weak dose-response relationship, there is need for well-conducted epidemiology studies.

Study	Objective	Resources Searched and Inclusion Criteria	Results	Conclusions as Reported by Study Authors
Franceschi and La Vecchia 1994[150]	To evaluate alcohol consumption and the risk of cancers of the stomach and colon-rectum.	Evidence base: 34 studies (15 cohort, 19 case-control).	Among the 15 *cohort studies*: seven studies were not very informative; and overall evidence from 8 studies showed colon cancer RR estimates varying within a narrow range of 1.0-1.7 [ranging between 1.1-1.3 in most studies], and rectal cancer 1.0-2.5 [ranging between 1.0-1.7 in most studies]. Among the 19 *case-control* studies: five studies were totally negative, and showed no evidence of association; 3 other studies showed overall significant associations; and remaining 11 studies showed no consistent overall association.	Epidemiology evidence regarding a causal role of alcoholic beverage consumption and colorectal carcinogenesis remains inconclusive.

Reported Mechanisms in the Epidemiology Literature

A search of the literature identified the following mechanisms reported in breast and colorectal cancer epidemiology studies that were not included in our primary evidence base (see Table 3 and Table 4, respectively). These studies investigated the association between alcohol consumption and increased cancer risk primarily by administering questionnaires to study dietary behavior and amount of alcohol consumption and correlated these findings with cancer incidence. Some of these studies looked at different alcoholic beverages, for example wine, beer, and other spirits. However, none of these studies controlled alcohol exposure.

Our searches of the literature identified hypothesis-generating studies that provide indirect evidence of potential mechanisms. These studies examined various metabolic pathways that have been proposed as potential connections between alcohol exposure and increased breast or colorectal cancer risk (see Table 5 and Table 6, respectively).

These hypothesis-generating studies and epidemiology studies were incorporated into this report in order to review and discuss this literature base in comparison with our primary evidence base.

Table 3. Breast cancer epidemiology studies

Proposed Mechanism	References
Changes in circulating hormone levels	[37,151-158]
DNA-adduct formation	[159]
Changes in levels of insulin-like growth factor	[160]
Changes in levels of biomarkers of inflammation	[77-81]
Cytochrome P450 polymorphism	[161,162]
Methylenetetrahydrofolate reductase polymorphism/Dietary/Vitamins	[38,163-173]
Alcohol dehydrogenase/Acetaldehyde dehydrogenase polymorphism	[45,47-50,174-178]
Other types of polymorphism	[179-184]

Table 4. Colorectal cancer epidemiology studies

Proposed Mechanism	References
DNA repair polymorphisms	[90,166,185-234]
Hyperproliferation of rectal mucosa	[141,235]
Colonic microbial metabolism resulting in the generation of acetaldehyde	[55,56]
Cytochrome P450 polymorphism	[236-240]
Alcohol dehydrogenase and acetaldehyde dehydrogenase polymorphism	[19,241-252]
Changes in levels of insulin-like growth factor	[253-256]
Impact of C-reactive protein and Inflammation	[257,258]
Methylenetetrahydrofolate reductase polymorphism/Dietary/Vitamins	[189,259-263]
Other types of polymorphism and mechanisms	[259,264-294]

Table 5. Hypothesis-generating breast cancer studies

Study	Reported Mechanism
Marietta et al. 2009[295]	Stimulation of Fanconi anemia–breast cancer associated (FANC–BRCA) DNA damage response network by acetaldehyde
Taibi et al. 2009[296]	Low levels of both xanthine dehydrogenase and cellular retinol binding protein
Jin et al. 2008[297]	Activation of BRCA2 transcription by estrogen receptor-beta
Maciel et al. 2004[298]	Inhibition of bioactivation of ethanol to acetaldehyde by folic acid
Jordao et al. 2004[299]	Increased lipid peroxidation
Stevens et al. 2000[300]	Change in estrogen levels
Colantoni et al. 2000[301]	Increased levels of malondialdehyde
Jones et al. 1998[302]	Response of MCF-7 cells to potential estrogens and non-estrogenic substances

Table 6. Hypothesis-generating colorectal cancer studies

Study	Reported Mechanism
Jelski et al. 2004[15]	Alcohol dehydrogenase and aldehyde dehydrogenase polymorphisms
Vincon et al. 2003[303]	Generation of free radicals.
Leuratti et al. 2002[304]	DNA adduct formation
Parlesak et al. 2000[305]	Inhibition of retinol oxidation
Koivisto et al. 1996[306]	Alcohol dehydrogenase polymorphism
Jokelainen et al. 1996[57]	Generation of acetaldehyde by human colonic bacteria
Seitz et al. 1996[21]	Alcohol dehydrogenase polymorphism
Nosova et al., 1996[307]	Generation of acetaldehyde by human colonic bacteria
Rosenberg et al. 1994[308]	Induction of cytochrome P450
Jokelainen et al. 1994[309]	Generation of acetaldehyde by human colonic bacteria
Shimizu et al. 1990[310]	Induction of cytochrome P450

Ongoing Clinical Trials

A search of the clinicaltrials.gov (http://clinicaltrials.gov/) Web site did not identify any ongoing trials related alcohol consumption and possible causal mechanisms for breast and colorectal cancers.

Chapter 4. Discussion

Breast Cancer

Key Question 1. What are the likely causal mechanisms by which alcohol contributes to the development of breast cancer? Which of the possible mechanisms (e.g., induction of P450 cytochromes and carcinogen metabolism, effects on blood hormone concentrations, effect of acetaldehyde or other alcohol metabolite on apoptosis and DNA repair, interactive effects on other nutritional factors, or others) are likely to be most important in breast cancer development?

Alcohol-related Changes in Circulating Hormones

Changes in circulating hormone levels due to chronic alcohol intake have been demonstrated in several epidemiology studies (see Table 3). Our searches identified eight epidemiology studies that looked at this connection.[37,151-157] Seven studies[151-157] made specific reference that moderate alcohol consumption may be responsible for increasing breast cancer risk by influencing hormonal levels and estrogen receptors and one study[37] reported light-to-moderate alcohol consumption was not associated with increase breast cancer risk. The findings from these seven studies suggest that alcohol interferes with estrogen pathways, thereby causing changes in hormonal levels and estrogen receptors. This may then have a direct effect on breast tissue and cancer risk. Given this apparent connection between alcohol intake and alterations in circulating hormones seen in the epidemiology literature, we looked for hypothesis-generating studies that examined this connection.

A majority of the human and animal studies identified in our searches and included in our primary evidence base also point to a connection between alcohol intake and changes in blood hormone levels, especially elevated levels of estrogen-related hormones in humans (see Table C-1 in Appendix C) and animals (see Table C-2 in Appendix C). Several cell line studies also suggest that estrogen receptor pathways may be altered by ethanol (see Table C-3 in Appendix C). Increased estrogen levels may increase the risk of breast cancer through increases in cell proliferation and alterations in estrogen receptors. Suzuki et al.[142] looked at the possible connection between estrogen receptor (ER) alterations, alcohol intake, and the risk of breast cancer in a meta-analysis of epidemiology studies (see Table 1.). The highest versus the lowest alcohol consumption categories were analyzed for their association with all ER+ and ER- subtype tumors. Meta-analysis of all studies using relative risk (RR) indicated a statistically significant 27% higher risk of developing ER+ tumors (95% CI: 1.17 to 1.38) and a 14% higher risk for developing ER- tumors (95% CI: 1.03 to 1.26) in the high consumption group. The authors concluded that they had “found support for a positive relationship between alcohol consumption and the development of all ER+ tumors.” The authors also concluded that “The results from these meta-analyses suggest that the biological mechanism for development of breast cancer due to alcohol intake could be explained not only through ER-mediated classical estrogen-dependent pathway but also through other mechanisms” such as DNA damage or increased expression of other signaling pathways leading to cell proliferation. These studies (human, animal, and cell line) combine to suggest that estrogen-related mechanisms may be altered by alcohol consumption and provide a potential causal mechanism by which alcohol affects the estrogen receptors thereby contributing to the increased risk of development of breast cancer.

Elevation in prolactin levels was examined in one human study. Ginsburg et al.[87] reported that serum prolactin levels increased in menopausal women during acute ethanol ingestion. In animal studies, ethanol-induced hyperprolactinemia in mice was associated with the development of mammary tumors.[97,98] While not as extensive as the estrogen-related studies, these studies give some indication that alcohol consumption may alter prolactin levels and increase the risk of developing breast cancer.

Cell Proliferation and Tumor Progression

Although we did not identify any epidemiology study that reported on hyperproliferation as a possible mechanism, enhancement of cell proliferation and tumor progression related to ethanol consumption and conversion to acetaldehyde and its connection to breast cancer has been examined in numerous animal (Table C-2 in Appendix C) and cell line studies (Table C-3 in Appendix C). Several of the animal studies used carcinogens such as MNU[93,94] or DMBA.[100,101,105] However, the DMBA studies were not as consistent in showing a relationship between ethanol and mammary tumorigenesis as the MNU studies (see Table C-2 in Appendix C). The effect of ethanol on cell proliferation in cell lines was examined in three studies included in this report. Izevbigie et al.[51] reported that ethanol stimulated cell proliferation in the MCF-7 cell line, Zhu et al.[109] reported that ethanol induced changes that could promote cancer development in the T4TD cell line, and Przylipiak et al.[110] reported that ethanol had direct growth stimulatory effects on the MCH cell line. Enhancement of cell proliferation and tumor progression as a potential causal mechanism linking ethanol and breast cancer has some support but human subject studies are needed to further explore this connection. According to Dumitrescu and Shields, estrogen-induced breast cancer may be as a result of cell proliferation, activation of CYP2E1, and DNA damage.[10]

Polymorphism in Ethanol Metabolism

Our searches identified a number of epidemiology studies proposing that both genetic and enzyme polymorphisms contribute to the promotion of breast cancer development in individuals who consume alcohol (see Table 3). Polymorphisms examined in these studies include cytochrome P450,[161,162] methylenetetrahydrofolate reductase,[38,163-173] and alcohol dehydrogenase and acetaldehyde dehydrogenase.[45,47-50,174-178] The majority of these studies reported enzyme polymorphism as a risk marker for breast cancer following moderate alcohol consumption. Our searches did not identify any experimental studies in humans or animals that examined this issue.

DNA Adduct Formation

DNA adduct formation was examined in an epidemiology study by Rundle et al.[159] The authors investigated the association between alcohol consumption and DNA adduct levels in breast tissue in women diagnosed with ductal carcinoma *in situ* and invasive ductal or lobular cancer (i.e., cases) vs. women with benign conditions without atypia (i.e., controls). In tumor and nontumor tissue from cases, adduct levels were increased among drinkers compared to nondrinkers. However, among controls, no increase in adduct levels were found regardless of drinking status.[159]

We identified no experimental human studies that examined this mechanism. We did identify experimental studies using animals that suggest intake of ethanol does increase adduct formation and could contribute to breast cancer risk.[96] Cell line studies also suggested that the formation of DNA adducts increases after incubation with ethanol.[107,108]

Other Potential Mechanisms

A single human study by Hartman et al.[76] reported on increased level of biomarkers of oxidative stress such as α-tocopherol and isoprostane after alcohol consumption (see Table C-1 in Appendix C). Our searches identified five epidemiology studies[77-81] that also postulated a connection between biomarkers of inflammation, alcohol intake, and risk of breast cancer. Increased levels of biomarkers such as malondialdehyde,[77,79] isoprostanes,[81] and catalase activity[78,80] were reported. We did not identify any experimental studies using animal or cell line models that examined other potential mechanisms.

Key Question 2. For the most likely mechanisms of action involving alcohol and the development of breast cancer, how might other factors modify the effect of alcohol on breast cancer (for example, age, latency of effect, intensity, duration, and recency of exposure, presence of co-carcinogens, presence of threshold effect)? Do the causal mechanisms vary by cell type or other tumor characteristics?

For this Key Question, we looked for studies that evaluated factors that modify the association of alcohol with biomarkers of risk of breast cancer. The human studies of alcohol consumption and hormone changes were performed in pre- and postmenopausal women but an actual age effect was not examined in these studies. The duration of consumption was relatively short; long term effects could not be calculated in these studies. However, we did identify one human study that examined biomarkers of oxidative stress and risk of carcinogenesis. Hartman et al. reported that in postmenopausal women who consumed 30 g alcohol per day, α-tocopherol decreased by 4.6% and isoprostane levels increased by 4.9%.[76] This study provides a possible link between oxidative stress and risk of breast cancer formation.

Table 7 and Table 8 contain an overview of the breast cancer studies included in this report in terms of study design and reporting issues that determined whether the study provides evidence of a direct or an indirect association between alcohol consumption and breast cancer. Route of administration, rate of absorption and metabolism, formulation and quantity of ethanol, and timing of the intervention, however, may reduce the generalizability of animal studies to a clinical setting. Although we evaluated cell line studies as part of our overall evidence evaluation, we did not include them in this table given that events such as confounding exposure, control for other risk factors, and cancer formation are not applicable to this model.

Table 7. Overall results from human breast cancer studies

Study	*Confounding Exposure	Cancer Formation	Surrogate Outcome Measure	Authors Reported on Causal Mechanism	Number of Links in the Pathway of Carcinogenesis
Hartman et al. 2005[76]	N	N	Y	Y	1
Dorgan et al. 2001[85] Same as [311]	N	N	Y	Y	1
Ginsburg et al. 1996[88]	N	N	Y	Y	1
Ginsburg et al. 1995[87]	N	N	Y	Y	1
Reichman et al. 1993[86]	N	N	Y	Y	1

*Confounding exposure: did study administer a carcinogen and /or acetaldehyde?

Y: there was confounding exposure
N: there was no confounding exposure

Table 8. Overall results from animal breast cancer studies

Study	*Confounding Exposure	Cancer Formation	Surrogate Outcome Measure	Authors Reported on Causal Mechanism	Number of Links in the Pathway of Carcinogenesis
Hilakivi-Clarke et al. 2004[92]	Y	Y	N	Y	1
Castro et al. 2003[95]	N	N	Y	Y	1
Chhabra et al. 2000[96]	Y	N	Y	Y	1
Watabiki et al. 2000[97]	N	N	Y	Y	1
Holmberg et al. 1995[91]	N	Y	N	N	0
Singletary et al. 1995[93]	Y	N	Y	N	0
Singletary and McNary 1994[94]	Y	N	Y	Y	1
Taylor et al. 1993[99]	Y	N	Y	Y	1
McDermott et al. 1992[101]	Y	Y	N	N	0
Hackney et al. 1992[102]	N	Y	N	N	0
Singletary and McNary 1994[104]	N	N	Y	Y	1
Singletary et al. 1991[105]	Y	N	Y	Y	1
Rogers and Conner 1990[100]	Y	Y	N	N	0
Grubbs et al. 1988[103]	Y	Y	N	N	1
Schrauzer et al. 1979[98]	Y	N	Y	Y	1

*Confounding exposure: did study administer a carcinogen and /or acetaldehyde?

Y: there was confounding exposure
N: there was no confounding exposure

Colorectal Cancer

Key Question 3. What are the likely causal mechanisms by which alcohol contributes to the development of colorectal cancer? Which of the possible mechanisms (e.g., induction of P450 cytochromes and carcinogen metabolism, effects on blood hormone concentrations, effect of acetaldehyde or other alcohol metabolite on apoptosis and DNA repair, interactive effects on other nutritional factors, or others) are likely to be most important in colorectal cancer development?

Acetaldehyde production in the colon. Exposure of colon mucosa to acetaldehyde from microbial metabolism of ethanol has been postulated as a mechanism for increasing the risk of developing colorectal cancer in two epidemiology studies (see Table 4)[55,56] and three experimental studies (see Table 5).[57,307,309] According to study authors, individual variations in human colonic flora may contribute to the risk of alcohol-related colorectal cancer,[55] and increased activity of intracolonic bacterial alcohol dehydrogenase may also play a role in increasing cancer risk.[56,57,307,309]

Experimental human studies examining this subject are few (see Table C-4 in Appendix C). A study by Basuroy et al.[83] suggests that acetaldehyde disrupts epithelial tight junction and cell adhesion and through this mechanism increases the risk of colon cancer. Several animal studies also looked at the effects of acetaldehyde in the colon (see Table C-5 in Appendix C). These studies showed mucosal damage after ethanol consumption,[120] increased degradation of folate,[70] stimulation of rectal carcinogenesis,[122] and an increased effect of carcinogens in the presence of acetaldehyde.[123] In cell line studies acetaldehyde exposure was reported to influence the initial steps of colonic carcinogenesis and later tumor development[136] and decrease the activity of some brush border enzymes.[137] Finally, a study using animal and cell line tissue found evidence that acetaldehyde stimulates cell proliferation in animal intestinal crypt cells and therefore acetaldehyde may act as a cocarcinogen in the colon.[141] These studies suggest that acetaldehyde production in the colon may provide a potential causal mechanism by which alcohol contributes to the development of colon cancer.

Cell proliferation. Hyperproliferation of rectal mucosa after exposure to alcohol was postulated as a mechanism for increasing the risk of developing colorectal cancer in an epidemiology study by Simanowski et al.[235] The authors examined rectal biopsies for proliferation markers such as histone H3 and Ki67 in 44 heavy drinkers and 26 controls. Heavy drinkers showed an increase in cell proliferation markers in the rectal mucosa compared to controls.[235]

An effect of ethanol consumption on cell proliferation in the colon was investigated in both animal and cell line studies in our primary evidence base. Several animal studies reported enhanced growth of mucosal tissue after chronic ethanol consumption.[125-127] Cell studies indicated that exposure to ethanol and acetaldehyde increases cell proliferation[74,136] and damages DNA which may contribute to cancer development.[135] Together these studies suggest that ethanol and acetaldehyde exposure in the colorectal mucosa may increase cell proliferation and be a potential mechanism connecting alcohol consumption to colorectal cancer risk.

DNA repair polymorphism. We identified 52 epidemiology studies that assessed DNA repair polymorphism and alcohol consumption. The majority of these studies suggested that DNA repair polymorphism may influence the risk of colorectal cancer.

Enzyme polymorphism. We identified 19 studies that assessed enzyme polymorphism in epidemiology studies: 13 examined alcohol and acetaldehyde dehydrogenase polymorphism;[19,241-252] five examined cytochrome P450 polymorphism;[236-240] and six examined methylenetetrahydrofolate reductase polymorphism.[189,259-263] The majority of these studies reported enzyme polymorphism as a risk marker for colorectal cancer following moderate alcohol consumption.

Other potential mechanisms. Ethanol may also influence carcinogenesis in the colon and rectum through an interaction with carcinogens. Animal studies suggest that ethanol exposure in the colon increases the chances of tumor development,[132] but other studies found no association between ethanol ingestion and colorectal carcinogenesis or instead reported inhibition of tumorigenesis.[73,130,131] Other possible mechanisms reported in animal studies include alcohol's inhibition of folate metabolism[70] and DNA hypomethylation.[124]

Key Question 4. For the most likely mechanisms of action involving alcohol and the development of colorectal cancer, how might other factors modify the effect of alcohol on colorectal cancer (for example, age, latency of effect, intensity, duration, and recency of exposure, presence of co-carcinogens, presence of threshold effect)? Do the causal mechanisms vary by cell type or other tumor characteristics?

For this Key Question, we looked for studies that evaluated factors that modify the association of alcohol with biomarkers of colorectal cancer risk. Few studies are available that examined factors that modify the effects of ethanol consumption on the risk of developing colorectal cancer. The study in human subjects in which biopsy samples were examined for damage after exposure to acetaldehyde did not report the influence of personal factors on the degree of damage generated.[83]

Table 9 and Table 10 contain an overview of the colorectal cancer studies included in this report in terms of study design and reporting issues that determined whether the study provides evidence of a direct or an indirect association between alcohol consumption and colorectal cancer. Route of administration, rate of absorption and metabolism, formulation and quantity of ethanol, and timing of the intervention however may reduce the generalizability of animal studies to a clinical setting. Although we evaluated cell line studies as part of our overall evidence evaluation, we did not include them in this table given that events such as confounding exposure, control for other risk factors, and cancer formation are not applicable to this model.

Table 9. Overall results from human colorectal cancer study

Study	*Confounding Exposure	Cancer Formation	Surrogate Outcome Measure	Authors Reported on Causal Mechanism	Number of Links in the Pathway of Carcinogenesis
Basuroy et al. 2005[83]	Y	N	Y	Y	1

*Confounding exposure: did study administer a carcinogen and/or acetaldehyde?

Y: there was confounding exposure
N: there was no confounding exposure

Table 10. Overall results from animal colorectal cancer studies

Study	*Confounding Exposure	Cancer Formation	Surrogate Outcome Measure	Authors Reported on Causal Mechanism	Number of Links in the Pathway of Carcinogenesis
Hayashi et al. 2007[118]	Y	N	Y	Y	1
Perez-Holanda et al. 2005[73]	Y	N	N	N	0
Pronko et al. 2002[120]	N	N	Y	Y	1
Roy et al. 2002[121]	N	N	Y	N	1
Homann et al. 2000[70]	N	N	Y	N	1
Choi et al. 1999[124]	N	N	Y	Y	1
Hakkak et al. 1996[119]	N	N	Y	Y	1
Simanowski et al. 1994[125]	N	N	Y	Y	1
Niwa et al. 1991[126]	Y	N	Y	Y	1
Seitz et al. 1990[122]	Y	N	Y	Y	1
McGarrity et al. 1988[129]	Y	N	Y	Y	1
Hamilton et al. 1988[130]	Y	N	Y	Y	1
Garzon et al. 1987[128]	Y	Y	N	Y	1
Hamilton et al. 1987[132]	Y	N	Y	Y	1
Hamilton et al. 1987[131]	Y	N	Y	Y	1
Simanowski et al. 1986[127]	N	N	Y	Y	1
Nelson et al. 1985[116]	Y	N	N	N	0
Seitz et al. 1985[123]	Y	N	Y	Y	1
Howarth et al. 1984[117]	Y	N	N	N	0

*Confounding exposure: did study administer a carcinogen and/or acetaldehyde?

Y: there was confounding exposure
N: there was no confounding exposure

Excluded Studies

Because this is a systematic review using specific inclusion and exclusion criteria with the creation of specific Key Questions, the report is directed at evidence that addresses each Key Question. None of the excluded studies (see Table D-1 in Appendix D) were left out for quality, design, conduct, integrity, or inaccuracy but rather because they did not address these Key Questions.

Future Research Goals

Our examination of the epidemiology literature correlating alcohol consumption with cancer risk has suggested many areas in which experimental research may provide insight into the actual mechanisms connecting cancer risk and alcohol consumption. For breast cancer these potential mechanisms are changes in circulating hormone levels and changes in hormone receptors, DNA-adduct formation, and various enzyme polymorphisms related to alcohol metabolism. For colorectal cancer these areas are DNA repair polymorphisms, mucosal cell proliferation, and various enzyme polymorphisms related to alcohol metabolism. Experimental studies in humans, animals, or cell lines have provided basic information on some but not all of these potential mechanisms.

The connection between alcohol intake and changes in estrogen levels and breast cancer risk has been studied in human, animal, and cell line studies. Future research in this area would seem to be warranted to determine the exact level of risk imposed by this pathway. A connection between cell proliferation and tumor progression in breast cancer has been suggested by animal studies but not in human studies and human-based studies in this area would seem to be warranted. Enzyme polymorphism in ethanol metabolism as well as in other metabolic pathways that may be influenced by alcohol may require more human-based studies as opposed to animal studies where polymorphism is not a factor. DNA adduct formation has not been well studied in human or animal studies and research in this area should be expanded. Oxidative stress and inflammation associated with alcohol consumption have been postulated as risk factors in epidemiology studies but not studied to any extent in hypothesis-generating studies. Oxidative stress and inflammation should be examined with better experimentally controlled studies.

Experimental human studies examining the connection between alcohol intake and colorectal cancer are few. Many potential mechanisms related to acetaldehyde production in the colon, cell proliferation due to ethanol or acetaldehyde exposure, alterations in DNA repair mechanisms, and the influence of carcinogens and alcohol in the colon need to be examined in human-based studies. Animal studies are also needed to examine the influence of bacterial flora, the effects of ethanol and acetaldehyde on the colon, especially changes in cell proliferation and DNA, and the interaction between carcinogens and ethanol and acetaldehyde.

Conclusions

Based on our systematic review of the literature, many potential mechanisms by which alcohol may influence the development of breast or colorectal cancers have been explored but the exact connection or connections remain unclear. The evidence points in several directions but the importance of any one mechanism is not apparent at this time.

Table 11 through Table 13 summarizes the mechanisms on alcohol consumption and the risk of breast cancer as presented in studies identified in this report. Six human, five animal and five cell line studies reported on changes in hormonal levels as the potential causal mechanism by which alcohol consumption may contribute to the development of breast cancer. Our findings are comparable to the most commonly reported mechanisms in most of the breast cancer epidemiology studies summarized in Table 3.

Table 11. Reported mechanisms in human breast cancer studies

Mechanism Reported by Study Authors	Number of Studies	References
Change in levels of estrogen, progesterone, and DHEA	2	85,311
Change in level of estrogen	1	88
Elevation of prolactin	1	87
Elevation of estrogens and DHEA	1	86

Table 12. Reported mechanisms in animal breast cancer studies

Mechanism Reported by Study Authors	Number of Studies	References
Change in level of estrogen	3	92-94
Biotransformation of ethanol to acetaldehyde	1	95
Formation of DNA adducts	1	96
Elevation of prolactin	2	97,98
Effects on DNA synthesis	2	104,105
Suppression of cellular immunity	1	99

Table 13. Reported mechanisms in cell line breast cancer studies

Mechanism Reported by Study Authors	Number of Studies	References
Effect on estrogen receptor- α expression	5	65,67-69,106
Effect on peroxisome proliferator-activated receptor (PPAR)-α and PPAR-β transactivation	1	115
Formation of DNA adducts	2	107,108
Disruption and modulation of cell proliferation	2	51,109
Upregulation of transcription of smooth muscle myosin alkali light chain	1	114
Upregulation of mammary gland mucin	1	113
Direct growth stimulatory effect by enhancement on 3H-thymidine	1	110
Change in potassium channels	1	112
Increase cAMP levels	1	111

Table 14 through Table 17 summarizes the mechanisms of alcohol consumption and the risk of colorectal cancer as presented in studies identified in this report. One human study exposed colonic mucosa biopsies to vapor-phase acetaldehyde and reported an effect of acetaldehyde on cell adhesion as the most likely causal mechanisms by which alcohol consumption may contribute to the development of colorectal cancer. In contrast, nine animal studies reported a local toxic effect of acetaldehyde resulting in mucosal damage as the most likely causal mechanism by which alcohol consumption may contribute to development of colorectal cancer. Other mechanisms identified in this report include:

- increase in cytochrome P4502E1 expression (two animal studies)
- effect on DNA synthesis and methylation (two animal studies, two cell line studies)
- effect on cell proliferation (two cell line studies)
- apoptotic cell death (three cell line studies)
- effect on various stages of carcinogenesis (two animal studies)
- changes in polyamine content (one animal study)
- effect of acetaldehyde on brush border enzymes (one cell line study)
- modulation of gene expression (one cell line study).

Our findings are comparable to some of the most common mechanisms (e.g., colonic microbial production of acetaldehyde, effect on DNA methylation and synthesis) reported by the colorectal cancer epidemiology studies summarized in Table 4.

Table 14. Reported mechanisms in human colorectal cancer study

Mechanism Reported by Study Authors	Number of Studies	References
Effect of acetaldehyde on cell to cell adhesion	1	83

Table 15. Reported mechanisms in animal colorectal cancer studies

Mechanism Reported by Study Authors	Number of Studies	References
Local toxic effect of acetaldehyde resulting in mucosal damage and cell proliferation	9	70,120-123,125-128
Increase cytochrome P4502EI expression	2	118,119
DNA methylation and synthesis	2	132,139
Effect on various stages of carcinogenesis	2	130,131
Changes in polyamine content	1	129

Table 16. Reported mechanisms in cell line colorectal cancer studies

Mechanism Reported by Study Authors	Number of Studies	References
Effect on DNA methylation and synthesis	2	134,140
Apoptotic cell death	3	75,133,134
Effect on cell proliferation	3	74,136,138
Effect of acetaldehyde on brush border enzyme	1	137
Modulation of gene expression	1	139

Table 17. Reported mechanisms in combination (animal, cell lines) colorectal cancer study

Mechanism Reported by Study Authors	Number of Studies	References
Effect on cell proliferation	1	141

Limitations

The evidence base for the report included 66 studies:

- six human studies (five breast cancer, one colorectal cancer)
- 34 animal studies (15 breast cancer, 19 colorectal cancer)
- 25 cell line studies (15 breast cancer, 10 colorectal cancer)

- one combination study (animal, cell line) on colorectal cancer.

Therefore the evidence in support of any potential mechanism connecting alcohol intake to cancer development is based largely on animal models. Animal models are important tools for understanding disease mechanisms but they have limitations when predicting the actual course of events in humans.[82] Reviews of animal studies have shown that there is a tendency to publish studies with positive results and not to publish studies that suggest no difference in measured outcomes (i.e., publication bias). Therefore studies that could possibly rule out mechanisms connecting alcohol and cancer may not be published. Positive results in animal studies may not translate to a clinical setting because carcinogens were administered in a controlled setting that is not characteristic of human conditions. Most experimental animals are young and rarely have comorbidities, a situation that may also limit generalizability of animal studies to clinical studies.[312]

Few human studies met the inclusion criteria for this report and this limited the comparisons that could be made between the findings of animal studies and those in human studies. Exact alcohol exposure can be controlled in animal studies but few human studies have done the same. While the four breast cancer human studies actually administered and quantified the amount of ethanol, the only colorectal cancer study administered acetaldehyde to biopsied colonic mucosa. Because of the limited number of human studies in our evidence base, we did look at potential mechanisms suggested in epidemiology studies and compared them to mechanisms examined in animal and cell line studies.

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List of Acronyms/Abbreviations

ADH: alcohol dehydrogenase
ALDH: aldehyde dehydrogenase
AJ: adherens junctions
AMMN: acetoxymethyl-methylnitrosamine
AOM: azoxymethane
BPDE: benzo[a]pyrene diolepoxide
BRCA1: breast cancer type 1
cAMP: cyclic adenosine monophosphate
CM: colonic mucosa
CY: cyanamide
CYP2E1: cytochromes P450 2E1
DHEA: dehydroepiandrosterone
DHEAS: DHEA sulfate
DMBA: dimethylene (a) anthracene
DMH: 1,1-dimethylhydrazine
DNA: deoxyribonucleic acid
EGFR: epidermal growth factor receptor
ER: estrogen receptor
ERT: estrogen replacement therapy
FCS: fetal calf serum
HLA: human leukocyte antigen
H_2O_2: hydrogen peroxide
H_2O: water
JACC: Japan Collaborative Cohort Study
JPHC: Japan Public Health Center-based Prospective Study
MAA: mutagenic malondialdehyde-acetaldehyde
MAM: methylazoxymethanol
MEOS: microsomal ethanol-oxidizing system
MLC: myosin alkali light chain
MNU: N-methyl-N-nitrosurea
NAD: nicotinamide adenine dinucleotide
NADH: reduced nicotinamide adenine dinucleotide
NMDA: N-nitrosodimethylamine
NNK: 4-methylnitrosoamino-1-3-pyridyl-1-butanone
PK: protein kinase
PPAR: peroxisome proliferator-activated receptor
PR: progesterone receptor
ROS: reactive oxygen species
rp: ribosomal protein
SAM: s-adenosylmethionine
TNF: tumor necrosis factor
TJ: tight junctions

Appendix A: Exact Search Strings

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
Cancerlit	1935 - September 18, 2009	www.pubmed.gov
ClinicalTrials.gov	Searched February 1, 2009	www.clinicaltrials.gov
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2010, Issue 1	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2010, Issue 1	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2010, Issue 1	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2010, Issue 1	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through May 3, 2010	OVID
Health Technology Assessment Database (HTA)	Through 2010, Issue 1	www.thecochranelibrary.com
MEDLINE	1965 through May 3, 2010	OVID
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2010, Issue 1	www.thecochranelibrary.com

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions:

OVID

$	=	truncation character (wildcard)
exp	=	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
/	=	limit controlled vocabulary heading
.fs.	=	floating subheading
.hw.	=	limit to heading word
.md.	=	type of methodology (PsycINFO)
.mp.	=	combined search fields (default if no fields are specified)
.pt.	=	publication type
.ti.	=	limit to title
.tw.	=	limit to title and abstract fields

PubMed

[mh]	=	MeSH heading
[majr]	=	MeSH heading designated as major topic
[pt]	=	publication type
[sb]	=	subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)
[sh]	=	MeSH subheading (qualifiers used in conjunction with MeSH headings)
[tiab]	=	keyword in title or abstract

Topic-specific search terms – alphabetical listing

Concept	Controlled Vocabulary	Keywords
Adrenal	Adrenal.hw. exp Adrenal gland/ exp Adrenal glands/ exp Endocrine system/	Adrenal Aldosterone Endocrine gland$ Primary hyperaldosteroneism
Alcohol	Alcohol Alcohol abstinence Alcohol drinking exp Alcohol-related disorders exp Alcoholic beverage exp Alcoholic beverages Alcohol metabolism Drinking behavior Ethanol Feeding behavior Food habits Temperance	Abstinence Alcohol$ Beer Brandy Cocktail$ EtOH Gin Liqueur$ Liquor$ Mixed drink$ Schnapps Spirits Vodka
Biochemical Processes	Exp biochemical processes/	
Breast cancer	exp breast cancer Breast carcinoma exp Breast diseases exp Breast neoplasms	Breast$ Cancer$ Carcinoma$ Lesion$ Lump$ Mammar$ Tumo?r$
Colorectal cancer	Adenomatous polyp Colorectal cancer Colorectal carcinoma Exp colorectal neoplasms	Cancer$ Carcinoma$ Colon$ Colorectal Lesion$ Polyp$ Rectal Rectum Tumo?r$
Experimental neoplasms	Experimental neoplasm/ exp Neoplasms, experimental/	

Concept	Controlled Vocabulary	Keywords
Hypothalamic-hypophyseal system	Hypothalamo-hypophyseal system Hypothalamus hypophysis system Pituitary gland	Hypothalamus hypophysis gonad system
Microbes	Achlorhydria/ Bacteria, aerobic Candida albicans Colon flora Intestine flora Microbial growth Microbiology.fs. microorganism	Bacteria Bacteriocolonic Flora Microb$ Microflora Yeast$
Oncogenesis	Breast carcinogenesis Chemical carcinogenesis Colorectal carcinogenesis Malignant neoplastic disease exp neoplastic processes exp Oncogenesis and malignant transformation	Carcinogenesis Oncogenesis Tumorigenesis Tumorigenic effect
Potential mechanisms	5,10 methlyenetetrahydrofolate reductase (FADH2) Acetaldehyde Alcohol dehydrogenase Aldehyde dehydrogenase ALDH2 Apoptosis Calcium signaling Cell cycle Cell cycle regulation Cell division Cell membrane permeability Cell nucleus Cell proliferation Cyclin dependent kinase 2 cyp2E1 Cytochrome p-450 enzyme system cytochrome p450 17 cytochrome p450 1A1 cytochrome p450 1A2	Acetaldehyde$ MAPK MAPKs NFkappaB Proto-oncogene Reactive oxygen

Concept	Controlled Vocabulary	Keywords
	cytochrome P450 1B1 cytochrome P-450 CYP1A1 cytochrome P-450 CYP1A2 cytochrome P-450 CYP2B1 cytochrome P-450 CYP2D6 cytochrome P-450 CYP2E1 cytochrome P-450 CYP3A Deamination DNA adducts exp DNA-binding proteins DNA damage Down regulation Estrogen activity Estrogen metabolism Estrogen receptor, alpha Estrogen receptor beta Fas antigen Folate metabolism exp Folic acid Folic acid Folic acid deficiency Gene control exp Gene expression regulation Gene function Gene mutation Genetic code Genetic polymorphism Genetic variability Growth regulation modulation hydroxylation MAP kinase signaling system Metabolism.fs. Methionine synthase Mitochondria exp Mitogen-activated kinases Mitogen activated protein kinase NF-kappa B Oxidative phosphorylation Oxidative stress	

Concept	Controlled Vocabulary	Keywords
	p16 protein human.sn. Polymorphism, genetic Protein expression Protein p16 Proto oncogene Exp reactive nitrogen species Reactive oxygen metabolite Exp Reactive oxygen species Receptor cross talk Receptor upregulation exp Receptors, estrogen exp Receptors, retinoic acid Retinoid Retinoic acid receptor beta exp Signal transduction exp Transferases Tretinoin	

EMBASE/MEDLINE

English language, remove overlap

Set Number	Concept	Search Statement
1	**Alcohol**	Alcohol drinking/ or exp alcohol-related disorders/ or alcohol metabolism/
2		exp alcoholic beverage/ or exp alcoholic beverages/ or alcohol/ or ethanol/ or beer or wine or alcohol$ or brandy$ or gin or vodka or schnapps or EtOH or liquor$ or liqueur$ or spirits or mixed drink$ or cocktail$
3		Drinking behavior/ or food habits/ or feeding behavior/ or temperance/ or alcohol abstinence/ or abstinence
4	Combine sets	or/1-3
	Oncogenesis	
5	Carcinogenesis	Exp neoplastic processes/ or exp oncogenesis and malignant transformation/ or malignant neoplastic disease/ or breast carcinogenesis/ or colorectal carcinogenesis/ or chemical carcinogenesis/ or exp neoplasms, experimental/ or experimental neoplasms
6		Carcinogenesis or oncogenesis or tumorigenesis or tumorigenic effect
7	Combine sets	or/5-6
	Potential mechanisms	
8		Proto oncogene/ or proto-oncogene or exp DNA-binding proteins/
9		Metabolism.fs. or deamination/
10	Signaling	Receptor cross-talk/ or exp signal transduction/ or calcium signaling/ or exp gene expression regulation/ or down regulation/ or protein expression/ or receptor upregulation/ or growth regulation modulation/
11	Estrogen	Estrogen receptor, alpha/ or exp receptors, estrogen/ or estrogen activity/ or estrogen metabolism/ or estrogen receptor beta/
12	MAPK	Exp mitogen-activated kinases/ or MAP kinase signaling system/ or mitogen activated protein kinase/ or MAPK or MAPKs
13	Cytochrome P-450	Cytochrome p-450 enzyme system/ or cyp2E1/ or cytochrome P450 17/ or cytochrome P450 1A1/ or cytochrome P450 1A2/ or cytochrome P450 1B1/ or cytochrome P-450 CYP1A1/ or cytochrome P-450 CYP1A2/ or cytochrome P-450 CYP2B1/ or cytochrome P-450 CYP2D6/ or cytochrome P-450 CYP2E1/ or cytochrome P-450 CYP3A/
14	Dehydrogenases	Alcohol dehydrogenase/ or aldehyde dehydrogenase/ or ALDH2/ or acetaldehyde$
15	Methylation	exp Folic acid/ or Folic acid/ or folic acid deficiency/ or folate metabolism/
16		DNA methylation/ or RNA methylation/ or DNA hypermethylation/ or DNA hypomethylation/ or methylation
17		Methionine synthase/

Set Number	Concept	Search Statement
18		Cyclin dependent kinase 2/ or Fas antigen/ or 5,10 methlyenetetrahydrofolate reductase FADH2/ or Protein p16/ or p16 protein human.nm.
19	Cells	Apoptosis/ or cell division/ or cell proliferation/ or cell cycle/ or cell cycle arrest/ or cell cycle regulation/ or cell membrane permeability/ or cell nucleus/
20	Misc. genetic concepts	Gene control/ or gene function/ or gene mutation/ or genetic code/ or genetic polymorphism/ or genetic variability/ or polymorphism, genetic/
21	DNA	DNA adducts/ or DNA damage/ or mitochondria/ or exp DNA-binding proteins/
22	Oxidation	Reactive oxygen metabolite/ or oxidative stress/ or hydroxylation/ or exp reactive oxygen species/ or oxidative phosphorylation/ or reactive oxygen or exp reactive nitrogen species/
23	Retinoic acid	Retinoid/ or retinoic acid receptor beta/ or exp receptors, retinoic acid/ or tretinoin/
24		NF-kappa B/ or NFkappaB
25		Exp transferases/
26	Acetaldehyde	Exp acetaldehyde/ or acetaldehyde$
27	Biochemical processes (includes DNA repair)	Exp biochemical processes/
28	Adrenal	Exp Adrenal gland/ or exp adrenal glands/ or adrenal.hw. or adrenal.tw. or aldosterone or primary hyperaldosteroneism or exp endocrine system/ or endocrine gland$
29	Hypothalamic	Hypothalamo-hypophyseal system/ or hypothalamus hypophysis system/ or Hypothalamus hypophysis gonad system or pituitary gland/
30	Microbial	Microflora or microbiology.fs. or microb$.ti. or achlorhydria/ or bacteria, aerobic/ or candida albicans/ or colon flora/ or intestine flora/ or microbial growth/ or microorganism/ or bacteria or bacteriocolonic or flora or Microflora or yeast$
31	Combine sets (mechanisms)	or/8-30
32	**Breast cancer**	exp Breast neoplasms/ or exp breast diseases/ or exp breast cancer/ or breast carcinoma/
33		(breast or mammar$) and (tumo?r$ or lesion$ or cancer$ or carcinoma$ or lump$)
34	Combine sets (breast cancer)	or/32 -33

Set Number	Concept	Search Statement
35	**Colorectal cancer**	Exp colorectal neoplasms/ or adenomatous polyp/ or colorectal cancer/ or colorectal carcinoma/
36		(colon$ or rectal or rectum or colorectal) and (tumo?r$ or lesion$ or cancer$ or carcinoma$ or polyp$)
37	Combine sets (colorectal cancer)	or/35-36
38	Combine sets Alcohol, oncogenesis & breast cancer	4 and 7 and 34
39	Combine sets Alcohol, mechanisms & breast cancer	4 and 31 and 34
40	Combine sets Alcohol, oncogenesis & colorectal cancer	4 and 7 and 37
41	Combine sets Alcohol, mechanisms & colorectal cancer	4 and 31 and 37
42	Combine sets	38 or 39 or 40 or 41
43	Limit to English	42 and English
44	Non-English	42 not 43
45	Eliminate overlap	Remove duplicates from 43

Appendix B: Sample Data Abstraction Forms

Level 1 – Abstract Review: At this review level abstracts were examined to determine if a document should be retrieved for further review. Checking the inclusion boxes in the form automatically led to retrieval of the full article. All documents selected for inclusion at this level fell to the next level for evaluation.

Keywords: **Abstract:**	Submit Data 1. Include or Exclude document Include Exclude Include: Non-English Language Clear Selection Submit Data

Level 2 – Full Document Review: At this level we made the final determination as to whether the document was to be excluded or included in the report. The reason for exclusion was noted in a separate box on the form. All documents selected for inclusion at this level fell to the next level for evaluation.

Keywords: **Abstract:**	Submit Data 1. Is this document included in the Report (includes Background and Evidence)? Include in Report Exclude Clear Selection 2. Reason for Exclusion Enlarge Shrink Submit Data

Level 3 – Background Document Review: At this level we determined if the document will appear in the Background section of the report or in the Evidence section of the report. If the document was to be used as background material this form was used to indicate which area in the Background section the document belonged. All documents selected for inclusion in the evidence report at this level fell to the next level for evaluation.

Submit Data

1. Is this document included in the Background only or the Evidence Report?

- ○ Include in Evidence Report
- ○ Include in Background Only

Clear Selection

2. If Included for Background only, which of the following apply?

- ☐ Basic cancer mechanisms
- ☐ Breast cancer mechanisms
- ☐ Colorectal cancer mechanisms
- ☐ Alcohol metabolism
- ☐ Epidemiology of alcohol and cancer
- ☐ Other components of alcoholic drinks

<u>Level 4</u> <u>– Evidence Base Document Review</u>: Only documents that were used in the evidence report appeared at this level. Information recorded at this level was used to organize the documents into specific areas of study depending on study design.

Submit Data
1. Which of the following apply to this document? ☐ Human studies - breast ☐ Animal models - breast ☐ Animal tissues - breast ☐ Cell lines - breast ☐ Human studies - colorectal ☐ Animal models - colorectal ☐ Animal tissues - colorectal ☐ Cell lines - colorectal Submit Data

Table B-1. Data abstraction and data management

Document ID#: internal ECRI Institute ID number
Article Citation
Country where study was completed
Year in which the study was performed
Experimental Model: type of animal model or cell line
Primary Mechanism examined: mechanism being tested for relationship between alcohol intake and cancer risk
Secondary Mechanism examined: for studies that explore multiple mechanisms
Amount of Alcohol Exposure: levels of alcohol exposure depending on the design of the experiment and the experimental model
Mode of Administration: mode of administration of alcohol depending on the design of the experiment and the experimental model
Duration of Alcohol Exposure: duration of alcohol exposure depending on the design of the experiment and the experimental model
Use of a Carcinogen: the carcinogenic agent, if any, being examined in the study along with alcohol
Use of other non-carcinogen agents: nutritional or other interventional agents utilized to show the relationship between alcohol intake and cancer risk
Description of subject characteristics in human studies: age, male/female ratio, smoking, comorbidities, race/ethnicity, alcoholism
Study design: explains the type of study design
Duration of the study
Direct or Indirect Association: explains evidence of carcinogenesis
Results for Intermediate Outcomes: usually molecular, biochemical, or histological outcomes which may be indicative of a direct or indirect relationship between alcohol intake and cancer risk
Results for Clinical Outcomes: typically broader organ measurements that correlate to a direct or indirect relationship between alcohol intake and cancer risk
Results for Patient Oriented Outcomes: entries in this column are only for human studies
Conclusions: did the study present evidence for or against the proposed mechanism

Appendix C: Evidence Tables

Evidence Base for Breast Cancer

Table C-1. Summary of results from human studies on breast cancer

Study	Model	Study Design	Mechanism Examined	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Hartman et al. 2005[76]	53 postmenopausal women	Case control	Increase levels of biomarkers of oxidative stress	Controlled diet plus each of three treatments (15 or 30 g alcohol per day or no-alcohol placebo beverage), during three 8-week periods in random order	After adjusting for body mass index (all models) and total serum cholesterol (tocopherol and isoprostane models), there was a 4.6% decrease (p = 0.02) in α-tocopherol and a 4.9% increase (p = 0.07) in isoprostane levels when women consumed 30 g alcohol/day (p = 0.06 and 0.05 for overall effect of alcohol on a-tocopherol and isoprostanes, respectively).	Moderate alcohol consumption increases some biomarkers of oxidative stress in postmenopausal women.

Study	Model	Study Design	Mechanism Examined	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Dorgan et al. 2001[85] Same as [311]	51 healthy postmenopausal women not using hormone replacement therapy	Three-period crossover design	Elevated serum levels of estradiol, estrone, estrone sulfate, testosterone, androstenedione, progesterone, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenediol	15 g or 30 g of alcohol per day or an alcohol-free placebo beverage through a three 8-week dietary period. Alcohol was supplied as 95% ethanol in 12 oz orange juice. Each dietary period was preceded by a 2- to 5-week washout period when participants did not consume any alcohol.	15 g of alcohol/day resulted in an increase of 7.5% (95% confidence interval [CI]: -0.3 to 15.9%; $p = 0.06$) of estrone sulfate. 30 g of alcohol/day resulted in an increase of 10.7% (95% CI: 2.7 to 19.3%; $p = 0.009$) estrone sulfate 15 g of alcohol/day resulted in an increase of 5.1% (95% CI: 1.4 to 9.0%; $p = 0.008$) DHEAS. 30 g of alcohol/day resulted in an increase of 7.5% (95% CI: 3.7 to 11.5%; $p < 0.001$) DHEAS	Results suggest a possible mechanism by which consumption of one or two alcoholic drinks per day by postmenopausal women could increase their risk of breast cancer.

Study	Model	Study Design	Mechanism Examined	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Ginsburg et al. 1996[88]	12 postmenopausal women receiving oral estrogen (estradiol, 1 mg/day) and progestin (medroxy-progesterone acetate) replacement therapy were compared with 12 postmenopausal women who were not using estrogen replacement therapy (ERT).	Randomized, double-blind, placebo-controlled crossover study	Effects of alcohol ingestion on estrogens in postmenopausal women	Pineapple juice and 40% ethanol at a dose of 2.2 mL/kg of body weight (0.7 g/kg of body weight) in a total volume of 300 mL over 15 minutes	Within 50 minutes of alcohol ingestion in postmenopausal women on ERT, there was a 3-fold increase in estradiol levels from 297 to 973 pmol/L ($p < 0.001$) No changes in estradiol following alcohol ingestion in postmenopausal women not on ERT	Acute alcohol ingestion may lead to significant and sustained elevations in circulating estradiol.
Ginsburg et al. 1995[87]	14 menopausal women using transdermal estradiol	Two randomized crossover studies	Effect of acute ethanol ingestion on prolactin in menopausal women using estradiol replacement	Ethanol (1 mL/kg, 95% ethanol) over 20 minutes	Alcohol when compared to isocaloric carbohydrate drink ingestion resulted in increased serum prolactin levels in both study 1 ($p < 0.03$) and study 2 ($p < 0.001$)	There was an increase in serum prolactin levels.

Study	Model	Study Design	Mechanism Examined	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Reichman et al. 1993[86]	34 premenopausal women with a history of regular menstrual cycle	Randomized, diet-controlled crossover intervention	The effects of alcohol consumption on plasma and urinary hormone (DHEA, estrogens) concentrations in premenopausal women	30 g of ethanol daily for three menstrual cycles and no alcohol for the other three	Plasma DHEAS levels increased by 7.0% ($p = 0.05$) in the follicular phase Plasma estrone levels increased by 21.2% ($p = 0.01$) in the peri-ovulatory phase Plasma estradiol increased by 27.5% ($p = 0.01$), urinary estradiol increased by 31.9% ($p = 0.009$) in the peri-ovulatory phase At the luteal phase, urinary estrone increased by 15.2% ($p = 0.05$), estradiol levels increased by 21.6% ($p = 0.02$), and estriol levels increased by 29.1% ($p = 0.03$)	Results suggest a possible mechanism between alcohol consumption and risk of breast cancer.

Table C-2. Summary of results from animal studies on breast cancer

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Hilakivi-Clarke et al. 2004[92]	Elevated levels of estrogen receptors	Rats	Amount in study groups: 0 g/kg ethanol vs. 16 g/kg ethanol vs. 25 g/kg ethanol Duration of Exposure: 12 days	Dimethylene(a)anthracene (DMBA)	Latency to the appearance of first tumor [weeks, mean ([s.e.m)] was 9.7 (0.6) in the control, 8.4 (0.5) in the 16 g alcohol group, and 8.6 (0.5) in the 25 g alcohol group. Tumor incidence and tumor multiplicity were higher in the alcohol groups compared to control. Tumor growth rate was similar in all three groups.	Maternal alcohol intake increased offspring's mammary tumorigenesis.
Castro et al. 2003[95]	Biotransformation of ethanol to acetaldehyde	Rats	Amount in study group: 0.21M ethanol Duration of exposure: 1 hour	None	Biotransformation of ethanol to acetaldehyde occurred in mammary tissue microsomes.	Result could have a significant effect in some stages of the process of breast tumor promotion by ethanol.
Chhabra et al. 2000[96]	Formation of DNA adducts	Rats	Amount in study group: 1.6 g/kg ethanol Duration of exposure: 14 days	N-nitrosodimethylamine (NDMA), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	There was a 10-fold increase in O^6-methylene adducts from NDMA in mammary gland following cotreatment with ethanol.	Nitrosamines and ethanol are contributors to mammary cancer risk and perinatal carcinogenesis.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Watabiki et al. 2000[97]	Ethanol-induced hyperprolactinemia and/or mammary tumor virus increased by the hyperprolactinemia	Rats	Amount in study groups: 10% ethanol vs. 15% ethanol vs. tap water Duration of exposure: 25 months	None	In the ethanol-treated group, tumor occurrence was reported in 9 (45%) of the 20 rats at 8 to 24 months. There no occurrence of tumor in the control.	The murine model may be useful to study the role of ethanol in mammary tumorigenesis.
Holmberg et al. 1995[91]	None reported	Rats	Amount in study groups: 1 ethanol vs. 3% ethanol Duration of exposure: 2 years	None	Following the administration of low amounts of ethanol, there was an increase in mammary gland fibroma, fibroadenoma or adenoma.	The finding seems not to be consistent in terms of a dose-response relationship or in their interrelation and may thus be regarded as an unspecific phenomenon.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Singletary et al. 1995[93]	Influence on initiation and promotion stages of carcinogenesis through change in blood estrogen and progesterone	Rats	Amount in study groups: Diet containing ethanol at 0% calories vs. 15% calories vs. 20% calories, vs. 30% calories Duration of exposure: 22 days	N-methyl-N-nitrosourea (MNU)	Ethanol consumption at 15% caloric intake resulted in an increase during either the initiation or promotion stages. Ethanol consumption at 20% caloric intake resulted in increase during the promotion stage There was no effect on either stage in the group that received ethanol at 30% caloric intake.	Ethanol at specific intakes can enhance the initiation and promotion stages of MNU-induced mammary tumorigenesis. However, there was not a consistent and proportionate increase in mammary tumor development with increasing intakes of ethanol.
Singletary and McNary 1994[94]	Effect on serum estradiol and progesterone	Rats	Amount in study groups: Diet containing ethanol at 0% calories vs. 20% calories, vs. 30% calories Duration of exposure: 35-39 days	MNU	Ethanol consumption at 20% caloric intake resulted in a 19% increase in rat mammary gland terminal-end bud (TEB) density and 49% decrease in alveolar bud (AVB) structures. Ethanol consumption at 30% caloric intake resulted in a 45% increase in rat mammary gland TEB density and 44% decrease in AVB structures.	Ethanol consumption can lead to an increase in the quantity of and the rate of cell proliferation of mammary gland terminal-end bud (TEB) structures.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Taylor et al. 1993[99]	Suppression of cellular immunity (T cell activation and proliferation, and on natural killer [NK] cytotoxicity)	Rats	Acute ethanol exposure of 2.5-3.5 g/kg body weight 1 hour before tumor inoculation vs. chronic consumption of liquid diet containing ethanol for 2 weeks before and for 3 weeks after tumor inoculation.	Study authors only reported "Tumor inoculation" by MADB106	Blood NK cytotoxic activity was reduced in ethanol treated rats. Number of blood large granular lymphocytes (LGL) per NK cells at 2 hours post ethanol administration dropped to 86% of control group and at 5 hours post ethanol administration: dropped to 74% of control group.	Alcohol exposure during fetal or adult life has profound immunopathological effects.
McDermott et al. 1992[101]	The aim of the study was to test the hypothesis that dietary alcohol intake increases the incidence of experimental mammary carcinoma	Rats	Amount in study groups: 4.4 g/kg/day ethanol vs. tap water Duration of exposure: 10 days	DMBA	Mean time (days, [SD] to first tumor appearance in the alcohol group was 63 (16.3) and 67.3 (19) in the control. Mean number of tumors/animal in the alcohol group was 3.2 (2.2) and 2.9 (2.7) in the control. Tumor rate growth (mm3/day) in the alcohol group was 30.7 (17.7) and 25.5 (11.8) in the control.	This study failed to support the hypothesis that dietary alcohol intake increases the incidence of mammary carcinoma.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Hackney et al. 1992[102]	Enhancement of the rate of mammary tumor development	Rats	Amount in study groups: 4 g/kg/day ethanol vs. 15 g/kg/day ethanol vs. 20 g/kg/day ethanol Duration of exposure: 65 weeks	None	There was no difference among study groups ($p = 0.10$) in development of mammary tumors.	Findings do not support the hypothesis that ethanol augments the risk of breast cancer.
Singletary and McNary 1994[104]	Effect on mammary gland structural development, DNA synthesis, and decrease in serum progesterone	Rats	Amount in study groups: Diet containing ethanol at 0% vs. 15% vs. 20% vs. 25% of calories Duration of exposure: Experiment 1: 32 days Experiment 2: 28 days Experiment 3: 33 days	None	In experiment 1, TEB increased for rats fed ethanol at 20% and 30% caloric intake and density of AVB decreased at all ethanol concentrations. In experiment 2, TEB density of ethanol-fed rats increased 64%. In experiment 3, there was no change in serum estradiol. However, serum progesterone: decreased by 56% and 51% compared to pair-fed control and ad lib-fed control rats, respectively.	Cancer risk in humans may be proportional to both cell number and rate of cell division within a target tissue.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Singletary et al. 1991[105]	Effect on mammary gland structural development and DNA synthesis	Rats	Amount in study groups: Diet containing ethanol at 0% vs. 15% vs. 20% vs. 30% of calories Duration of exposure: 29 days	DMBA	Rats that consumed ethanol at 10% and 20% of calories exhibited a significant increase in TEB density and a significant decrease in AVB density. Rats that consumed ethanol at 20% of total calories prior to DMBA administration exhibited a significant 54-74% increase in tumor incidence compared with rats fed the control diet. 78%, 82%, and 91% of tumor-bearing rats possessed adenocarcinomas for rats fed the diets containing 0%, 10%, and 20% of calories as ethanol, respectively. For rats fed ethanol at 30% of calories, tumor incidence was identical to that for rats fed the control diet until 12 weeks following DMBA dosing.	Specific quantities of ethanol can enhance the initiation and the promotion stages of DMBA-induced mammary tumorigenesis.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Rogers and Conner 1990[100]	Enhancement of carcinogenesis	Rats	Amount in study groups: Diet providing 10% vs. 20% vs. 50% of calories as ethanol Duration of exposure: Exp 1: 10% of ethanol for 1 week, 20% of alcohol for 3 weeks. Exp 2: 10% of ethanol for 4 days, 20% for the remainder of the experiment. Exp 3: 10% of ethanol for 4 weeks, at the beginning of the 4th week the rats were given a single dose of 50% ethanol.	DMBA	In all experiments, there was no detectable effect on mammary tumor latency, incidence, number, weight or histology.	There was no effect of ethanol on mammary gland tumorigenesis induced by DMBA.
Grubbs et al. 1988[103]	Enhancement of mammary cancer initiation	Rats	Amount in study groups: 7.0 g/kg ethanol vs. 3.5 g/kg ethanol Duration of exposure: DMBA group: 3 weeks MNU group: 8 weeks	DMBA MNU	Mammary cancer initiation by DMBA was increased by both dose levels of ethanol. Mammary cancer initiation by MNU was increased by high dose of ethanol.	Ethanol enhances mammary cancer initiation.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Schrauzer et al. 1979[98]	Change in prolactin levels	Mice	Amount in study groups: 12% ethanol vs. table wine with an alcohol content of 11.5% Duration of exposure: 6 weeks	Bittner virus	Mean serum prolactin levels (ng/ml [SD]) in the alcohol group was 23 (9) and 52 (23) in the control. Tumor incidence, growth rates and latency in the alcohol group occurred in 8 animals that developed adenocarcinoma, the first at the age of 6 months (after 5 months of exposure), the last at 11 months (median: 8). The tumor incidence was 73%. Among the control, animals developed mammary tumors between 12 and 16 months of age (median: 14.2). Tumor incidence was 82% * difference in latency times was significant ($p < 0.001$)	Long-term exposure to ethanol significantly reduced the latency period in the genesis of spontaneous mammary adenocarcinoma.

Table C-3. Summary of results from cell line studies on breast cancer

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Etique et al. 2009[106]	Cross-talk between A2A Adenosine receptor (A2A AR) and the estrogen receptor-alpha	MCF-7	Amount in study groups: 0.3% ethanol vs. 0.1% ethanol Duration of exposure: 24 hours	There was an increase in the level of progesterone receptor mRNA following 24 hours of treatment with 1uM CGS21680 (a selective agonist). Antagonist (MSX-3) induced a dose-dependent inhibition of an ethanol-induced increase in progesterone receptor expression.	Although results demonstrate cross-talk between A2A AR and estrogen receptor-alpha in the ethanol action on MCF-7 cells, the link between ethanol and A2A AR remains to be determined.
Venkata et al. 2008[115]	Relationship between ethanol and its metabolite acetaldehyde on peroxisome proliferator-activated receptor (PPAR)alpha and PPAR(beta) transactivation	MCF-7	Amount in study groups: 0 mM ethanol vs. 10 mM ethanol vs. 30 mM ethanol vs. 100 mM ethanol vs. 300 mM ethanol Duration of exposure: 24 hours	Over a range of ethanol concentrations up to 300mM, ethanol was able to dose dependently and significantly increase the expression of PPAR(alpha) mRNA in MCF-7 cells. Ethanol also modestly increased the mRNA for PPAR(beta) with a significant increase seen at 30 and 300mM, although not at 100mM. The increased expression for PPAR(beta) mRNA was only in the order of two-fold in contrast to the approximately sevenfold increase seen for PPAR(alpha) compared with the absence of ethanol.	There is likely to be a complex interplay in the way ethanol and/or acetaldehyde acts via the PPARs and other proteins to influence tumorigenic relevant pathways such as proliferation, resistance to apoptosis, and invasiveness.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Etique et al. 2007[68]	Activation of the estrogen signaling pathway (cyclic AMP [cAMP]/protein kinase A [PKA]).	MCF-7	Amount in study groups: 0.1% ethanol vs. 0.3% ethanol vs. 0.5% ethanol vs. 0.7% ethanol Duration of exposure: 24 hours	There was a significant 1.6-fold increase in progesterone receptor mRNA level for either 0.1 or 0.3% ethanol and a 1.3-fold increase in pS2 expression for a dose of 0.3%.	Ethanol treatment of MCF-7 breast cells stimulates the cAMP/PKA pathway which triggers two important events: an increase in the expression of genes with cAMP response element (CRE) in their promoter, like aromatase as well as a ligand-independent activation of estrogen receptor-alpha and transcription of target genes.
Etique et al. 2004[65]	Stimulation of cell proliferation, estrogen receptor-alpha, and aromatase expression	MCF-7	Amount in study groups: 0.0% ethanol vs. 0.1% ethanol vs. 0.3% ethanol Duration of exposure: Up to 6 days	Ethanol enhanced cell proliferation and clonal growth of MCF-7 cells. In the presence of 0.1% ethanol, there was a significant increase in cell proliferation (11.5%) at day 4 and it peaked at 28% at day 6. In the presence of 0.3% ethanol, there was a significant increase (11%) at day 4, and no significant change at day 6.	Study supports data suggesting that ethanol is an increased risk factor for breast cancer.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Izevbigie et al. 2002[51]	Disruption and modulation of cell proliferation	MCF-7	Ethanol (0.1%-10%) with or without an inhibitor of mitogen activated protein kinase 1 vs. 0.3%, 3%, and 10% ethanol for 5-, 10-, 20-, and 40-min time course experiments.	Exposure of to 65 mM (0.3% ethanol) increased incorporation of [3-H] thymidiene into MCF-7 cells by approximately two-fold over control. In contrast to the growth stimulatory effect of 0.3% ethanol, both 3% and 10% ethanol significantly inhibited cell growth.	Ethanol stimulates p44/42 mitogen-activated protein kinase's activity and subsequent MCF-7 cell proliferation.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Przylipiak et al. 1996[110]	Direct growth-stimulatory effect on cancer cells by enhancement of 3H-thymidine	MCF-7	Amount in study groups: 0.00001% ethanol vs. 0.0001% ethanol vs. 0.001% ethanol vs. 0.01% ethanol vs. 0.1% ethanol vs. 1% ethanol vs. 10% ethanol Duration of exposure: 5 hours	Ethanol enhanced 3H-thymidine uptake in cultured human mammary carcinoma cell line MCF-7. The most effective concentration was 0.01% which evoked a 202% enhancement of 3H-thymidine uptake, when compared to controls. Concentrations of ethanol between 0.0001% and 10% also significantly enhanced 3H-thymidine uptake. A concentration of 0.00001% ethanol did not affect thymidine incorporation.	Ethanol appears to play a role in tumor promotion in vivo as a result of direct growth-stimulatory effect on human mammary cancer cells in vitro.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Singletary et al. 2004[107]	Decreased capacity to remove benzo[a]pyrene diolepoxide-DNA (BPDE-DNA) adducts	MCF-10F	Amount in study groups: 0 mM ethanol vs. 15 mM ethanol vs. 25 mM ethanol Duration of exposure: 48 hours	Incubation of cells with ethanol was associated with a significant increase in prevalence of BPDE-DNA adducts compared to controls.	Ethanol- and oxidative stress-associated inhibition of carcinogen-DNA adduct removal in non-neoplastic human mammary cells may be another biological mechanism to explain the increased risk for breast cancer among women consuming alcohol.
Barnes et al. 2000[108]	DNA adduct formation and enhancement carcinogen-induced DNA damage in target cell DNA	MCF-10F	Amount in study groups: Ethanol: 0, 5, 15, or 25 mM vs. Aldehyde: 0, 0.5, 2.5, or 5.0 µM Duration of exposure: 6 days	Exposure of cells to physiologically relevant concentrations of either ethanol or aldehyde prior to dosing with B[a]P increased adducts formation.	A possible mechanism by which alcohol intake may be enhancing breast cancer risk in humans may be through an ethanol- and aldehyde-associated increase in carcinogen-DNA adducts in the target mammary epithelial cells.
Zhu et al. 2001[109]	Modulation of expression of ribosomal protein L7a (rpL7a)	T4TD	Amount in study groups: 100-400 mg/dl ethanol Duration of exposure: 16 days	Long-term exposure to ethanol (2 weeks) significantly reduced the transcript of rpL7a by more than 60%.	Ethanol-induced alteration of rpL7a expression may mediate the promoting effects of ethanol on breast cancer development.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Dhar and Plummer 2006[112]	Protein expression of G-protein inwardly rectifying potassium channels (GIRK)	MDA-MB-453	Amount in study group: 0.12% ethanol Duration of exposure: 16 hours	Transfection of GIRK1 or GIRK4 plasmids decreased gene expression in MDA-MB-453 breast cancer cells.	Functional GIRK channel exists in breast cancer cells that are involved in cellular signaling.
Singletary et al. 2001[69]	Proliferation and intracellular content of cAMP in estrogen receptor (ER)-alpha expression	MCF-7, ZR75.1, BT-20, MDA-MB-231	Amount in study groups: 0-100 mM ethanol Duration of exposure: Up to 10 days	Exposure of ER+ cell lines to increasing concentrations of ethanol was associated with an increase in cell proliferation. For example, ethanol added to cultures of cells at concentrations of 20-50 mM significantly stimulated proliferation of MCF-7 and ZR75.1 cells by 53-91% following 7 and 10 days of treatment, compared to controls.	Treatment with ethanol is associated with increased proliferation of two estrogen receptor-positive human breast cancer cell lines.
Zhu et al. 2001[114]	Up-regulation of transcription of smooth muscle myosin alkali light chain (MLC 1sm)	MCF-7, T47D, MDA-MB-231	Amount in study groups: 50-400 mg/dl ethanol Duration of exposure: 16 days	At 400 mg/dl, an ethanol-mediated increase was evident at 6 hours (55% increase), peaked at 24 hours (2.7 fold increase) following exposure. At pharmacologically relevant concentrations (e.g., 100 mg/dl), ethanol produced a significant increase of MLC 1sm expression, and progressively higher ethanol concentrations resulted in more up-regulation.	Alcohol consumption may promote the progression of breast cancer in women.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Fan et al. 2000[67]	Stimulation of the estrogen receptor signaling	MCF-7, T47D	Amount in study groups: 60 mM-100 mM ethanol Duration of exposure: 24 hours	Alcohol partially reverses the BRCA1-mediated inhibition of estrogen receptor-alpha transcriptional activity. Alcohol down-regulates BRCA1 and up-regulates estrogen receptor-alpha expression in MCF-7 cells.	Inactivation of BRCA1 and increased estrogen-responsiveness might contribute to alcohol-induced breast cancer.
Verna and Davidson 1999[113]	Mammary gland mucin (MUC1) upregulation	MCF-7, T84	Amount in study groups: 0 mM ethanol vs. 50 mM ethanol vs. 100 mM ethanol vs. 150 mM ethanol vs. 200 mM ethanol vs. 250 mM ethanol vs. 500 mM ethanol Duration of exposure: Acute exposure: 24 hours Chronic exposure: up to 4 weeks	Ethanol enhanced the expression of MUC1 mRNA in a dose- and time-dependent manner in MCF-7 cells.	Ethanol regulates expression of the MUC1 gene at the transcription level which strongly suggests the existence of ethanol responsive elements in the promoter of the mucin gene.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Cyong et al. 1978[111]	Increase cAMP levels	MM46 tumor cells	Amount in study groups: 0% vs. 0.1% vs. 0.5% vs. 1.0% vs. 2.5% vs. 5.0% ethanol Duration of exposure: 30 minutes	Dose-related increases in cAMP were observed at ethanol concentrations from 0.1% to 5.0%.	Results suggest that either tumor cell membrane, or its membrane-associated defense mechanism for detergents, may be incomplete.

Evidence Base for Colorectal Cancer

Table C-4. Summary of results from human studies on colorectal cancer

Study	Study Design	Mechanism Examined	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Basuroy et al. 2005[83]	Case series. Mucosal biopsies from the left colon (4 forceps biopsies from visibly normal area of mucosa in each subject) were collected from subjects admitted for colonoscopy for the purpose of cancer surveillance. Authors did not report patients' characteristics and previous alcohol exposure.	The effect of acetaldehyde on tyrosine phosphorylation, immmunofluorescence localization, and detergent-insoluble fractions of the tight junctions (TJ) and adherens junctions (AJ).	Biopsies were exposed to vapor-phase acetaldehyde, to achieve acetaldehyde concentration of 100-600 uM in the buffer bathing the tissue. Briefly, biopsies in 24-well culture plates were treated with vapor-phase acetaldehyde by placing stock acetaldehyde solution (0.1%-0.6%) in the reservoir wells and sealing the lid to the plate with tapes. 5 hours	Acetaldehyde resulted in epithelial TJ disruption by inducing tyrosine phosphorylation and dissociation from the cytoskeleton of TJ and AJ proteins.	These may have significant implications for the loss of cell-cell adhesion and increased risk for colon cancer.

Table C-5. Summary of results from animal studies on colorectal cancer

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Hayashi et al. 2007[118]	Increased expression of cytochrome P4502E1 (CYP2E1)	Rats	Amount in study group: Ethanol-containing liquid diet (36% of total calories, 5% ethanol v/v) Duration of exposure: 36 weeks	1,1-dimethylhydrazine (DMH)	The number of aberrant crypt foci (ACF) in colons obtained from ethanol-fed rats with DMH was 24, which was significantly more than that of the other treated rats.	The increased expression of CYP2E1 induced by chronic ethanol consumption promotes the development of DMH-induced colon cancer.
Perez-Holanda et al. 2005[73]	Effect of ethanol consumption on experimental colon carcinogenesis using a dynamic model with concomitant administration of alcohol and dimethylhydrazine (DMH).	Rats	Amount in study group: Ethanol at a dose of 1.23 g/kg of body weight Duration of exposure: 24 weeks	DMH	Tumors developed only in DMH treated groups: 25 rats (89%) in the DMH group and 16 rats (100%) in the DMH + ethanol group. However, when excluding tumor-free animals, no differences were observed in the mean number of tumors per rat (1.67 in the DMH group compared to 1.60 in the DMH + ethanol group).	Addition of an ethanol supplement does not modify colorectal carcinogenesis using a dynamic model of tumor induction with DMH.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Pronko et al. 2002[120]	Activities of alcohol dehydrogenase (ADH), catalase, microsomal ethanol-oxidizing system (MEOS), and aldehyde dehydrogenase (ALDH)	Rats	Amount in study group: Ethanol as 25% of calories Duration of exposure: 35 days	None	MEOS activity in the alcohol group was 149% higher compared to control group (increase not statistically significant). Effect of acute alcohol intoxication in rats consuming ethanol chronically (control vs. ethanol diet) as measured by ethanol concentrations in the colon was 9.1 (0.98) vs. 11.1 (1.52) and in the rectum was 13.6 (2.57) vs. 17.9 (2.90). Effect of acute alcohol intoxication in rats consuming ethanol chronically (control vs. ethanol diet) as measured by acetaldehyde concentrations in the colon was 7.93 (1.22) vs. 18.5 (3.94)* and in the rectum: 18.1 (3.95) vs. 30.5 (7.13). *$p < 0.05$	This mechanism can account for the local toxicity of ethanol after its chronic consumption, and relates the development of mucosal damage and compensatory hyper-regenerative processes, and possibly carcinogenesis, in the colonic and rectal mucosa of alcoholics to the effects of acetaldehyde.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Homann et al. 2000[70]	Folate deficiency via microbial acetaldehyde production	Rats	<u>Amount in study group</u>: 3 g/kg of ethanol <u>Duration of exposure</u>: 2 weeks	None	Alcohol treatment led to very high intracolonic acetaldehyde levels (387 [185] mM). Erythrocyte, serum and small intestinal folate levels were unaffected by alcohol treatment. Alcohol administration decreased significantly colonic mucosal folate levels by 48%.	Alcohol administration leads to local folate deficiency of colonic mucosa in rats, most probably via the degradation of folate by the high levels of acetaldehyde microbially produced from ethanol.
Choi et al. 1999[124]	DNA methylation and methylation of p53 tumor suppressor gene	Rats	<u>Amount in study group</u>: Diet containing 36% of total energy as ethanol <u>Duration of exposure</u>: 4 weeks	None	Titrated methyl uptake by colonic DNA from alcohol-fed rats was 57% less than that in control DNA ($p < 0.05$)	Genomic undermethylation of colonic DNA was observed in the alcohol-fed rats compared to control rats.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Hakkak et al. 1996[119]	The effects on expression of CYP2E1 and CYP2C7	Rats	Amount in study groups: 8-13 g/kg/day ethanol. Duration of exposure: Not reported by authors.	None	CYP2E1 was found to be present in the colon and induced by ethanol. Chronic ethanol treatment increased expression of both hepatic ($p < 0.01$) and colonic ($p < 0.05$) CYP2E1 by three-fold.	CYP2E1 and CYP2C7 are present in the colonic tissue and are inducible by ethanol.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Simanowski et al. 1994[125]	Effect on rectal cell proliferation (hyperregeneration)	Rats	Amount in study group: 36% of total calories as ethanol, with an additional acute intraperitoneal dose of 2.5 g/kg body weight Duration of exposure: 4 weeks	None	While age by itself did not affect colorectal cell renewal, chronic ethanol consumption stimulated rectal, but not colonic, crypt cell production rate in an age dependent manner. While no significant effect of ethanol was noted in young animals, cell proliferation was significantly enhanced in middle aged animals by 81% (95% CI: 4.1 (2.7-5.5) v 7.4 (6.0-8.7) cells/crypt/hour, *p <0.001*) and in old animals by 138% (95% CI: 4.5 (3.3-5.6) v 10.7 (8.9-12.4) cells/crypt/hour, *p <0.001*), after ethanol ingestion. There was a significant positive correlation between crypt cell production rate and acetaldehyde concentrations measured in the distal and proximal colon after an acute dose of ethanol.	Hyperregeneration of the rectal mucosa after alcohol drinking could by itself favor carcinogenesis, which is especially relevant in old age.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Niwa et al. 1991[126]	Hyperproliferation of rectosigmoidal colon	Rats	Amount in study groups: 7.5% ethanol vs. 10% ethanol vs. 15% ethanol Duration of exposure: 414 days	Methylazoxymethanol (MAM) acetate	Incidence of colonic cancer (11/17, 85%) was higher in the group that received 10% ethanol compared to control distilled water, $p = 0.04$.	A relatively short-term administration of ethanol induced significant hyperproliferation of the colonic, especially rectosigmoidal colonic, mucosa.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Seitz et al. 1990[122]	Acetaldehyde generation	Rats	Carcinogenesis Study 1 with a duration of exposure of 15 weeks: Liquid diet containing 36% of total calories as ethanol vs. isocaloric glucose Carcinogenesis Study II with a duration of exposure of 3 hrs: 2.5 ml 0.15 NaCl vs. 2.5 ml 0.15 NaCl + cyanamide (CY) vs. 2.5 ml ethanol vs. 2.5 ml ethanol + CY Acetaldehyde Determination in Blood and Tissues: Acute dose of ethanol (2.5 g/kg body wt)	Acetoxymethyl-methylnitrosamine (AMMN) CY	Using metaphase-arrest technique, administration of alcohol induced rectal (99.1 [2.0] vs. 9.1 [1.8] cells/crypt/hour, *p <0.01*), but not caecal (18.9 [1.3] vs. 22.2 [3.3]] cells/crypt/hour, *p <0.05*. Mucosal concentration of acetaldehyde (nmolg/colon)* in the rectum was 198 (23) and 120 (23) in the caecum. These values were not affected by chronic alcohol feeding. **p <0.05*	Chronic ethanol consumption can stimulate under certain experimental conditions chemically induced rectal carcinogenesis by direct mechanisms in the rectal mucosa, possibly mediated by acetaldehyde.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
McGarrity et al. 1988[129]	Changes in polyamine content	Rats	Amount in study group: Ethanol as 36% of total calories Duration of exposure: 16 weeks	DMH	DMH and DMH + ethanol groups developed 20 adenocarcinomas: with tumors located in the proximal colon (8 vs. 3), distal colon (11 vs. 114) and rectum (1 vs. 3) for the DMH and DMH + ethanol groups, respectively. No tumors developed in the control or ethanol treated groups.	Chronic ethanol consumption did not alter overall tumor formation, however consumption was reported to increase putrescine content in all 3 regions (proximal, distal colon and rectum) compared to the control liquid diet group. Increase in tissue putrescine levels may possibly reflect increased ornithine decarboxylase activity which has been shown to be increased in human colon adenocarcinomas and premalignant adenomas.
Hamilton et al. 1988[130]	Effect on the initiation phase of carcinogenesis	Rats	Amount in study group: Ethanol as 33% of total calories Duration of exposure: 13 weeks	Azoxymethane (AOM)	After 24 hours of AOM administration, levels of DNA adducts O^6-methylguanine and 7-methylguanine were reduced in the clonic mucosa of the ethanol-fed rats to 14 ±7% and 61 ±11% of controls.	Dietary ethanol during the preinduction and induction phase of the AOM model dramatically inhibits tumorigenesis.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Garzon et al. 1987[128]	Local effect of ethanol on the colorectal mucosa	Rats	Amount in study group: Liquid diets containing 36% of total calories as ethanol Duration of exposure: 10 weeks	AMMN	Significant difference in occurrence of colorectal tumors following chronic ethanol feeding at weeks 15 (42.1 vs. 15.8, $p < 0.05$). No significant difference was reported at weeks 18 and 21.	Chronic ethanol feeding combined with the direct acting carcinogen AMMN resulted in an earlier occurrence of colorectal tumors.
Hamilton et al. 1987[132]	Effect on fecal bacterial flora, and colonic epithelial DNA synthesis	Rats	Amount in study groups: Liquid diet containing 0% ethanol vs. 9% ethanol vs. 18% ethanol as calories Duration of exposure: 25 weeks	AOM	Low ethanol group demonstrated a trend for higher incidence of left-sided colonic tumors compared to controls (35% vs. 15% controls, $p = 0.06$). The total number of tumors in the high-ethanol group compared to controls was 46% vs. 81%, $p = 0.002$), respectively.	Modulation of experimental colonic tumorigenesis by ethanol consumption was due to alcohol rather than other beverage constituents.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Hamilton et al. 1987[131]	Effect on preinduction, induction, and postinduction phases of carcinogenesis	Rats	Amount in study groups: Liquid diet containing 11% ethanol vs. 22% ethanol vs. 33% ethanol as calories Duration of exposure: 13 weeks	AOM	Suppression of colonic tumorigenesis occurred in the groups with high levels of chronic dietary ethanol consumption during acclimatization and AOM administration: in the 33% and 22% diet groups, the prevalence of colonic tumors was 3% and 20% as compared with 50% in control (*p* <0.001 and p <0.02, respectively).	Chronic dietary ethanol effects on experimental colonic tumorigenesis with AOM are: (a) due to mechanisms affecting the preinduction and/or induction phase, including carcinogen metabolism; (b) unrelated to postinduction events such as tumor promotion and progression; and (c) dependent on ethanol dose with a threshold for inhibition of tumorigenesis which is mediated by ethanol inhibition of carcinogen metabolism.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Simanowski et al. 1986[127]	Promotion of cell proliferation	Rats	Amount in study group: Liquid diet containing 36% of total calories as ethanol (6.6% v/v) Duration of exposure: 4 weeks	None	Cell proliferation rate was 19.1 (2.0) in the ethanol fed group vs. 9.1 (1.8) cell/crypt/hour in the carbohydrate fed group, *p <0.005.* Serum gastrin also was elevated in the ethanol fed group 172 (51) vs. 106 (27) pmol/l, *p <0.01*).	The ethanol dependent proliferative changes in the rectal mucosa are predictive of higher susceptibility of this site to carcinogenesis, supporting experimental and epidemiology data. Increased gastrin concentrations may partly explain the observed rectal hyperproliferation. Other possible causes cannot, however, be excluded.
Nelson et al. 1985[116]	None reported by study authors	Rats	Amount in study groups: 95% laboratory grade ethanol diluted vs. tap water Duration of exposure: 19 weeks	DMH	Number of colonic tumors* in the DMH group was 77 and 88 in the DMH + ethanol group. *$p = 0.764$	No augmentation of colonic tumor induction in rats supplemented by dietary ethanol was seen.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Seitz et al. 1985[123]	Generation of acetaldehyde	Rats	Amount in study groups: Ethanol given as 36% of total calories; ethanol concentration of alcohol diet was 6.6% (v/v) vs. isocaloric carbohydrates Duration of exposure: 4 weeks	DMH	There was a 2.8 fold increase in rectal tumors on the ethanol fed rats compared to controls (*p* <0.02). All large intestinal tumors were located in the rectum in 47% of ethanol fed rats vs. 27% in controls.	The observed increase of ADH activity in the distal colorectum after chronic ethanol feeding may be of relevance with respect to the cocarcinogenic effect of ethanol in the rectum.
Howarth et al. 1984[117]	None reported by study authors	Rats	Amount in study groups: High-fat diet vs. Beer vs. Alcohol (4.8% v/v) Duration of exposure: 20 weeks	DMH	Alcohol did not affect the incidence of intestinal cancers. The shift of mean tumor distance toward the anus was similar in ethanol drinkers (0.61 [0.33] to 0.33 [0.23], *p* <0.05).	Alcohol had no effect in our syngeneic model of DMH-induced colorectal cancer, while a high-fat diet had a potent cocarcinogenic effect.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Roy et al. 2002[121]	Effect on cell proliferation, apoptosis, and formation of mutagenic malondialdehyde-acetaldehyde (MAA)	Mice	Amount in study group: Ethanol supplementation in the drinking water (15% alternating with 20% on a daily basis) Duration of exposure: 10 weeks	None	Ethanol supplementation resulted in a significant increase in tumor number (135± 35%, $p = 0.027$ vs. control). The induction of tumorigenesis by ethanol was most dramatic in the distal small bowel (167± 56%, $p = 0.001$).	Ethanol consumption is a risk factor for colorectal cancer.

Table C-6. Summary of results from cell line studies on colorectal cancer

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Lemos et al. 2007[140]	Modulation of folate uptake	Caco-2	Amount in study group: 12% alcohol Duration of exposure: Not reported	Ethanol had an acute inhibitory effect on both 3H-folic acid and 3H-methotrexate uptake.	Alcohol inhibited 3H-folic acid uptake in Caco-2 cells.
Rodriguez et al. 2004[75]	Increase in tumor necrosis factor-alpha receptor-1 (TNF-R1) levels	Caco-2	Amount in study groups: 25 mM ethanol vs. 50 mM ethanol vs. 100 mM ethanol Duration of exposure: 48 hours	Caco-2 cells showed a significant 80% increase in TNF-R1 levels at 200 mM ethanol ($p < 0.05$).	Exposure of intestinal cells to pharmacologic concentrations of ethanol increases TNF-R1 levels and may augment TNF-alpha-mediated cell injury.
Asai et al. 2003[134]	Intestinal epithelial cell death induced by acute, low concentrations of ethanol	Caco-2	Amount in study groups: 0% ethanol vs. 5% ethanol vs. 10% ethanol Duration of exposure: 3 hours	Treatment with 5% and 10% ethanol for 3 hours led to a gradual increase in phosphatidylserine (PS) externalization. Caspase-mediated CK18 was significantly enhanced as early as 1 hour after 10% ethanol incubation, while DNA fragmentation was detected from 2 hours onwards.	Apoptotic cell death in confluent Caco-2 cells was induced by acute and low concentrations of ethanol. These results suggest that clinically achievable doses of ethanol impair intestinal barrier function by induction of apoptosis in intestinal epithelial cells.
Tong et al. 1999[74]	Induction of epidermal growth factor receptor (EGFR) expression and mitogenesis	Caco-2	Amount in study group: 0.22 mM of ethanol Duration of exposure: 24 hours	Alcohol affects proliferation of Caco-2 cells, elevates EGFR expression and raises cyclin D1 mRNA and protein expression.	Low blood levels of alcohol may stimulate in vivo proliferation of colonocytes by elevating transcription of a growth factor receptor as well as modifying expression of a cell cycle regulator.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Koivisto and Salaspuro 1998[136]	Effect of acetaldehyde alone or in combination with ethanol on cell proliferation rate	Caco-2	Study 1: Acute exposure: cells were exposed to acetaldehyde and/or ethanol for 72 hours. Study 2: Chronic exposure: cells were grown in the presence of acetaldehyde and/or ethanol for five passages with daily change of media.	No significant differences were observed between the four groups in the cytotoxic studies (control vs. 100 mM ethanol vs. 500 uM acetaldehyde vs. 1,000 uM acetaldehyde) suggesting that a 72 hour treatment with 500 or 1,000 uM acetaldehyde, or 100 mM ethanol does not have cytotoxic effects on these cells. In the proliferation studies, the acute effect of acetaldehyde on the proliferation rate of Caco-2 cells was strongly inhibitory. The duplication time of Caco-2 cells was also significantly increased by acute exposure to 100 mM ethanol. Concomitant presence of ethanol did not, however, significantly alter the proliferation rate of acetaldehyde-treated cells. 5-week treatment with 500 uM acetaldehyde, both alone and in combination with 100 mM ethanol, significantly decreased cell duplication time as compared with control. A 5-week treatment with 100 mM alone did not have any significant effect on cell proliferation rate. Acetaldehyde decreased the adhesion of Caco-2 cells to both collagens 1 & IV in the cell adhesion studies.	Ethanol-driven or even endogenous acetaldehyde contributes to the initial steps of colonic carcinogenesis and has an effect on later tumor development.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Koivisto and Salaspuro 1997[137]	Effect of acetaldehyde on brush border enzyme activities	Caco-2	Amount in study groups: 500 uM acetaldehyde vs. 500 uM acetaldehyde + 100 mM ethanol vs. 1,000 uM acetaldehyde + 100 mM ethanol vs. 100 mM ethanol Duration of exposure: 13 days	Ethanol alone significantly increased the specific activities of sucrase and maltase, but no significant effect on lactase activity. Only ethanol increased alkaline phosphatase activity. Control cells, as well as cells grown in the presence of 100 mM ethanol alone or 500 uM acetaldehyde, showed a typical pattern of dome formation, with a sharp increase in the number of domes a few days after the confluency, followed by a rapid decrease and plateau. Cells grown in presence of both 100 mM ethanol and 1,000 uM acateladehyde showed significantly fewer domes 4 and 7 days after the confluency than control cells. The acetaldehyde dehydrogenase (ALDH) activity of Caco-2 cells, measured using 200 uM acetaldehyde as substrate was quite similar to that of normal colonic mucosa.	Acetaldehyde decreases the activities of some, but not all, brush border enzymes in Caco-2 cells.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Vaculova et al. 2004[133]	Modulation of the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced apoptosis	HT-29	Experiment 1: 4% ethanol alone or in combination for 4 or 24 h in the medium with 5% of fetal calf serum (FCS). Experiment 2: Using ethanol (0.1–6%) alone, the cells were treated for 48 hours.	There was only a limited cytotoxicity of TRAIL (100 ng/ml) in HT-29 cells. After 24-hour-treatment, the cell viability was 82%. However, when TRAIL was combined with ethanol, only 40% of cells remained viable. There was no significant changes in ethanol-treated cells and about two-fold enhancement of the number of cells with decreased MMP after TRAIL treatment (4 hours) compared to control were detected.	Ethanol acts as a potent agent, sensitizing colon cancer cells to TRAIL-induced apoptosis.
Blasiak et al. 2000[135]	Formation of crosslinks with DNA	Colonic mucosa (CM) cells	Single exposure study: CM cells were exposed to ethanol at 10 mm vs. acetaldehyde at 100 mm for 1 hour. Combined exposure study: In combined exposure, the cells were subsequently exposed to ethanol and acetaldehyde at all combinations of the concentrations of the agents for 1 hour	Ethanol caused DNA strand breaks. The CM cells exposed to ethanol at 100 mM were able to remove DNA damage within time period shorter than 2 hours.	Alcohol consumption may lead to the damage to DNA of gastrointestinal tract, which in turn can directly or indirectly contribute to the appearance and development of cancers of this organ.

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Results	Conclusions as Reported by Study Authors
Papavassiliou et al. 1994[139]	Modulation of human leukocyte antigen (HLA) class I gene expression	HT-29, SW-1116, HCT-15	Amount in study group: 100% ethanol Duration of exposure: 48 hours	Ethanol had no effect on the expression of HLA class 1 antigens in human colon adenocarcinoma cell lines. Ethanol (1.7×10^{-10} M to 1.7×10^{-1} M), had no effect on the expression of HLA class 1 antigens on these colonocytes, corresponding mRNA levels, or the expression of HLA constructs.	These findings do not support the hypothesis that ethanol may modulate the expression of HLA class 1 genes in human colon cancer cells.
Malagolini et al. 1994[138]	Differentiation of intestinal cells	Caco-2, HT-29	Amount in study groups: 0 mM ethanol vs. 50 mM ethanol vs. 100 mM ethanol vs. 200 mM ethanol Duration of exposure: 7 days	The addition of ethanol in the culture medium resulted in a significant increment of sucrase and alpha 2, 6-sialyltransferase activities in all cell lines, as well as the beta 1, 4-N-acetylgalactosaminyl-transferase activity in the Caco-2 cells and alkaline phosphatase activity in HT-29 cells.	Ethanol in vitro affects the differentiation of intestinal cells along the enterocytic lineage.

Table C-7. Summary of results from combination study (animal, cell line) on colorectal cancer

Study	Mechanism Examined	Experimental Model	Amount and Duration of Ethanol and/or Acetaldehyde Exposure	Use of Carcinogen	Results	Conclusions as Reported by Study Authors
Pannequin et al. 2007[141]	Accumulation of phosphatidylethanol resulting in a signal change in intestinal cell proliferation	Mice, Caco-2	Animal study: 2 mol/L (10%) ethanol for 4 months. Cell line study: 10 mmol/L of ethanol or 0.5 mmol/L of acetaldehyde once daily for 48 hours.	None	Chronic exposure to low doses of ethanol (10 mmol/L) induces an increase of maximal intestinal cell density.	The disruption of cellular signals might facilitate the stimulatory role of ethanol metabolites such as acetaldehyde on the proliferation of cells within intestinal crypts, thereby participating in the well-established cocarcinogenic role of alcohol consumption in the colon.

Appendix D: List of Excluded Studies

Table D-1. Excluded full articles

Study	Reason(s) for Exclusion
Yi et al. 2010[313]	Cancer mortality study.
Author(s) not listed 1988[103]	Clinical meeting article.
Purohit et al. 2005[40]	Clinical meeting article.
Scheppach et al. 1999[314]	Clinical meeting article.
Seitz et al. 1992[315]	Clinical meeting article.
Weisburger 1992[316]	Clinical meeting article.
Kleinjans et al. 1996[317]	Contents of alcoholic beverage.
Potter et al. 1982[318]	Correlation analysis study.
Siegmund et al. 2003[319]	Description of animal models in gastrointestinal alcohol research.
Aye et al. 2004[320]	Invasion of breast cancer cells.
Luo 2006[321]	Invasion of breast cancer cells.
Luo and Miller 2000[322]	Invasion of breast cancer cells.
Ma et al. 2003[323]	Invasion of breast cancer cells.
Meng et al. 2000[324]	Invasion of breast cancer cells.
McGarrity and Nelson 1986[325]	Letter to editor.
Larsen 1993[326]	News report publication.
Colombo et al. 2001[327]	No outcome of interest.
Fiala et al. 1987[328]	No outcome of interest.
Zedeck 1980[329]	No outcome of interest.
Holford 1987[5]	Pharmacokinetic study.
Weisburger and Wynder 1984[330]	Review article.
Agrawal et al. 2007[331]	Review article.
Alberts 2002[332]	Review article.
Ambrosone 2000[333]	Review article.
Arasaradnam et al. 2008[334]	Review article.
Author(s) not listed 2000[1]	Review article.
Author(s) not listed 2008[27]	Review article.
Author(s) not listed 1994[335]	Review article.
Baan et al. 2007[2]	Review article.

Study	Reason(s) for Exclusion
Bailey 2003[336]	Review article.
Blot 1992[337]	Review article.
Boffetta and Hashibe 2006[338]	Review article.
Bosetti et al. 2002[339]	Review article.
Brown 2005[340]	Review article.
Campos et al. 2005[341]	Review article.
Chhabra et al. 1996[342]	Review article.
Correa Lima and Gomes-da-Silva 2005[343]	Review article.
Dossus and Kaaks 2008,[344]	Review article.
Dumitrescu and Cotaria 2005[345]	Review article.
Ferguson et al. 2005[346]	Review article.
Filion 2002[347]	Review article.
Forman et al. 2004[348]	Review article.
Fraumeni 1979[349]	Review article.
Gago-Dominguez et al. 2007[350]	Review article.
Giovannucci 2002[351]	Review article.
Goodwin 2008[352]	Review article.
Hamid et al. 2009[353]	Review article.
Heavey et al. 2004[354]	Review article.
Homann et al. 2005[355]	Review article.
Huxley et al. 2007[356]	Review article.
Key and Verkasalo 1999[357]	Review article.
Key et al. 2004[42]	Review article.
Kim et al. 2007[358]	Review article.
Klatsky 2001[359]	Review article.
La Vecchia 1989[360]	Review article.
Lands 1998[361]	Review article.
Ledermann 1955[362]	Review article.
Li and Lai 2009[363]	Review article.
Lieber 2000[364]	Review article.
Lindhal 1992[365]	Review article.
Longnecker 1995[366]	Review article.

Study	Reason(s) for Exclusion
Longnecker 1995[367]	Review article.
Lowenfels 1990[368]	Review article.
Mason and Choi 2005[369]	Review article.
Nagy 2004[9]	Review article.
Nanri et al. 2007[370]	Review article.
O'Hanlon 2005[35]	Review article.
Payne 1990[371]	Review article.
Perse and Cerar 2007[84]	Review article.
Porter 1993[372]	Review article.
Porter 1995[373]	Review article.
Poschl and Seitz 2004[24]	Review article.
Poschl et al. 2004[374]	Review article.
Pufulete et al. 2003[375]	Review article.
Purohit 2000[376]	Review article.
Rampersaud et al. 2002[377]	Review article.
Rogers and Conner 1986[378]	Review article.
Rogers et al. 1993[379]	Review article.
Rothman et al. 1995[380]	Review article.
Sakar et al. 2001[381]	Review article.
Salaspuro 1996[20]	Review article.
Salaspuro and Mezey 2003[382]	Review article.
Schatzkin and Longnecker 1994[43]	Review article.
Secretan et al. 2009[17]	Review article.
Seitz and Becker 2007[383]	Review article.
Seitz and Homann 2007[384]	Review article.
Seitz and Maurer 2007[385]	Review article.
Seitz and Poschl 1997[386]	Review article.
Seitz et al. 1994[387]	Review article.
Seitz et al. 2005[369]	Review article.
Seitz et al. 1998[388]	Review article.
Siegmund et al. 2006[389]	Review article.
Simanowski et al. 1995[390]	Review article.

Study	Reason(s) for Exclusion
Stoll 1999[391]	Review article.
Tan et al. 2006[392]	Review article.
Taylor and Rehm 2006[393]	Review article.
Thies and Siegers 1989[394]	Review article.
Tsigris et al. 2007[395]	Review article.
Ulrich 2007[396]	Review article.
Walker and Burkitt 1976[397]	Review article.
Wang 2003[398]	Review article.
Wang 2005[399]	Review article.
Weisburger et al. 1981[400]	Review article.
Weisburger 1998[401]	Review article.
Welsch 1985[402]	Review article.
Williams 1976[403]	Review article.
Winawer and Shike 1992[404]	Review article.
Wright et al. 1999[25]	Review article.
Wynder 1977[405]	Review article.
Wynder 1978[406]	Review article
Nozawa et al. 2006[407]	Study administered freeze-dried beer.
Martin et al. 2004[408]	Study administered Resveratrol, a polyphenol found in grapes.
Gierer 1955[409]	Study did not look at cancer causation.
Briviba et al. 2002[410]	Study did not report on consumption/administration of ethanol.
Caderni et al. 2000[411]	Study did not report on consumption/administration of ethanol.
Cerda et al. 1999[412]	Study did not report on consumption/administration of ethanol.
Depeint et al. 2006[413]	Study did not report on consumption/administration of ethanol.
Diergaarde et al. 2003[259]	Study did not report on consumption/administration of ethanol.
Dolara et al. 2005[358]	Study did not report on consumption/administration of ethanol.
Farah 2005[414]	Study did not report on consumption/administration of ethanol.

Study	Reason(s) for Exclusion
Femia et al. 2005[415]	Study did not report on consumption/administration of ethanol.
Gonthier et al. 2003[416]	Study did not report on consumption/administration of ethanol.
Hall et al. 1991[417]	Study did not report on consumption/administration of ethanol.
Kabat and Rohan 2007[418]	Study did not report on consumption/administration of ethanol.
Kabat et al. 2007[419]	Study did not report on consumption/administration of ethanol.
Lagiou et al. 2009[420]	Study did not report on consumption/administration of ethanol.
Etique et al. 2004[421]	Study did not report on consumption/administration of ethanol.
Linz et al. 2004[422]	Study did not report on consumption/administration of ethanol.
Luceri et al. 2002[423]	Study did not report on consumption/administration of ethanol.
Maciel et al. 2004[298]	Study did not report on consumption/administration of ethanol.
Moon et al. 2006[424]	Study did not report on consumption/administration of ethanol.
Morris and Seifter 1992[425]	Study did not report on consumption/administration of ethanol.
Nozawa et al. 2004[426]	Study did not report on consumption/administration of ethanol.
Nozawa et al. 2004[427]	Study did not report on consumption/administration of ethanol.
Nozawa et al. 2005[428]	Study did not report on consumption/administration of ethanol.
Peluso et al. 2008[429]	Study did not report on consumption/administration of ethanol.
Reddy et al. 1997[430]	Study did not report on consumption/administration of ethanol.
Robson et al. 2006[431]	Study did not report on consumption/administration of ethanol.
Schrauzer et al. 1982[432]	Study did not report on consumption/administration of ethanol.
Takechi et al. 2004[433]	Study did not report on consumption/administration of ethanol.

Study	Reason(s) for Exclusion
Wulf et al. 2004[434]	Study did not report on consumption/administration of ethanol.
Yamagishi et al. 2002[435]	Study did not report on consumption/administration of ethanol.
Slattery et al. 2009[58]	Study looked at tumor markers.
Gago-Dominguez et al. 2005[436]	Unrelated epidemiology study.
Gaudet et al. 2005[437]	Unrelated epidemiology study.
Giacosa et al. 2004[438]	Unrelated epidemiology study.
Lewis et al. 2003[439]	Unrelated epidemiology study.
Orita et al. 2004[440]	Unrelated epidemiology study.
Schatzkin et al. 1993[441]	Unrelated epidemiology study.
Visapaa et al. 1998[442]	Inhibition of intracolonic acetaldehyde production by ciprofloxacin.
Vogel et al. 2007[184]	Title correction.

Appendix E: Peer Reviewers

List of peer reviewers to be provided by AHRQ.