Alcohol as a cause of Cancer

May 2008

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FOREWORD BY THE MINISTER

Cancer is a major burden on our community. In response, the NSW Government has made a major commitment to the control and cure of cancer. This commitment has seen the development of NSW Cancer Plan covering prevention, screening, treatment, research and information.

Many cancers are preventable and the risk of cancer can be reduced by avoiding risky behaviour. The NSW Cancer Plan 2007 — 2010 places emphasis on preventing future cancers and this report provides good evidence of the magnitude of the risk for alcohol and what we should do to reduce this risk.

It is quite difficult to change behaviour that is entrenched in individuals or our community. However, this report provides a compelling case that drinking behaviour places people at unnecessary risk and it is worth the effort to change.

I commend this report to you.

Hon. Verity Firth MP

Minister for Women
Minister for Science and Medical Research
Minister Assisting the Minister Health (Cancer)
Minister Assisting the Minister for Climate Change,
Environment and Water (Environment)

CHIEF CANCER OFFICER'S REPORT

Cancer is increasing in our society and has become the major burden of disease, outstripping cardiovascular disease[1,2]. It is also now the major cause of premature deaths, and the major cause of death, in the 45 to 65 year old age group.

Cancer could be prevented in about 35% of cases by modifying behaviour to largely avoid known cancer risk factors[3]. Top of the list is tobacco as the major cause of preventable disease in NSW.[4] However, a diet rich in processed or red meat, salt or salted fish, and obesity are known risk factors for cancer. Alternatively, physical activity, and a diet rich in fibre, fruit and vegetables leading to ideal body weight are known to protect against cancer.

Seventy-seven percent of NSW adults drink alcohol and are likely to associate it with celebrations, family gatherings and good times[5]. However, it is now quite clear that alcohol is carcinogenic for some types of cancer. Alcohol is classified as a cancer causing agent by the International Agency for Research on Cancer. It already imposes a significant health burden on our population with anti-social behaviour and trauma associated with excessive risky drinking. This report concentrates on alcohol causing cancer.

This report, *Alcohol as a cause of Cancer,* presents the results from a systematic review of the world's literature on alcohol and cancer and clearly shows that the consumption of alcohol, even at moderate levels, is associated with an increased risk of several cancers. These cancers include bowel cancer and breast cancer, the second and third most common cancers in NSW respectively. However, it also includes cancers of the upper aero-digestive tract including mouth and oesophageal cancer for which there is a substantial further increase in the risk of cancer when alcohol is combined with tobacco smoking.

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[1] Begg S, Voss T, Barber B, Stevenson C, Stanley L, Lopez AD. 2007. The burden of disease and injury in Australia PHE 82 Canberra : AIHW

[2] Australian Institute of Health and Welfare 2006. Australia's Health 2006 AIHW Cat No AH 573. Canberra AIHW

[3] Danaei G, Vander Hoorn S, Lopez AD, et al: Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 366:1784-93, 2005

[4] World Cancer Research Fund/American Institute of Cancer Research. Food, nutrition, physical activity and the prevention of cancer: A global perspective. Washington DC, AICR 2007

[5] Cotter T, Perez D, Dessaix A, Baker D, Murphy M, Crawford J, Denney J, Bishop JF. Cancer and Lifestyle Factors. Sydney: Cancer Institute NSW, December 2007

The risk alcohol poses for cancer is large. Four standard drinks a day increase the cancer risk by 22% or with eight standard drinks a day the cancer risk increases by 90%. For each standard drink per day, the risk of breast cancer specifically increases by around 10%.

The *NSW Cancer Plan 2007–2010*, places significant emphasis on effective cancer prevention with a key goal to promote behaviour to reduce risks and thus avoid cancer[6]. This report suggests that encouraging a reduction of alcohol consumption should be part of our strategy for cancer prevention in NSW. In 2006, 32.8% of NSW adults drank alcohol at levels which were classified as risky by the 2001 NHMRC guidelines[7]. Currently, only 41% of NSW adults are aware that drinking too much alcohol can cause cancer and 33% reject this notion outright[8]. Information about the association between alcohol and cancer needs to be more widely available so that the public can make informed choices about their behaviour. We hope the information in this report will encourage people to make positive changes to their lives so as to improve their health and subsequently reduce their risk of cancer.

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CHIEF CANCER OFFICER

CEO, CANCER INSTITUTE NSW

[6] NSW Cancer Plan 2007-2010

[7] NSW Department of Health: 2006 Report on Adult Health from the New South Wales Population Health Survey. Sydney, Centre for Epidemiology and Research, NSW Department of Health, 2007

[8] Cotter T, Perez D, Dessaix A, Baker D, Murphy M, Crawford J, Denney J, Bishop JF. Cancer and Lifestyle Factors. Sydney: Cancer Institute NSW, December 2007.

EXECUTIVE SUMMARY

Background

Alcohol consumption is a known risk factor for cancer and in 1988 alcohol was classified by the World Health Organization (WHO) International Agency for Research on Cancer (IARC) as a Group 1 carcinogen. This is the highest IARC classification for humans. Alcohol is a risk factor for cancers of the mouth, pharynx, larynx, oesophagus, and liver. The carcinogenicity of alcoholic beverages was reassessed by IARC in February 2007. The Working Group concluded that the occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colo-rectum and female breast were causally related to the consumption of alcoholic beverages.

The key national guidelines that outline recommendations in relation to alcohol consumption are published by the National Health and Medical Research Council (NHMRC). This guidance has recently been revised with the draft guidelines released in October 2007 for public consultation. The new guidelines recommend lower alcohol intake than the previous 2001 edition. The draft guidelines recommend that for low risk of both immediate and long-term harm from drinking, men and women should not exceed two standard drinks in any one day. This recommendation is consistent with that of the World Health Organization (WHO)[9]. However, it is important to recognise that this guidance takes into consideration all health risks and benefits associated with alcohol consumption. An increased risk of cancer may actually be evident at levels of alcohol intake classified by the NHMRC as 'low risk'. The draft guidance from the NHMRC states that alcohol is a cause of cancer of the mouth, throat and oesophagus, and is a risk factor for cancer of the stomach, breast, liver and pancreas, and it has also been associated with bowel cancer risk.

Objective

The aim of this literature review is to provide a summary of the current evidence relating to the relationship between alcohol consumption and cancer.

Methodology

A systematic literature search was undertaken to identify existing systematic reviews which examine the link between alcohol and specific cancer types. From this search, 634 reviews were identified of which 31 met the inclusion/exclusion criteria. Of these 31, seven were identified as key or supportive reviews, based on currency and quality. Whilst all 31 reviews were evaluated, the findings of the seven key papers were considered in detail. A second literature search was undertaken to identify original papers published subsequent to the key review for each cancer type. This search identified 1,149 citations, of which 58 were briefly reviewed to update and augment the key systematic reviews.

[9] In *Diet Nutrition and the prevention of chronic diseases*. Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series 916. 2003. World Health Organization: Geneva

Limitations

The evidence presented in this review is based on meta-analyses of epidemiological studies and there are limitations to keep in mind. Firstly, misclassification of exposure to alcohol is a common challenge. For example, light, infrequent, or ex-drinkers may all be classified as non-drinkers. Secondly, most studies are based on self-reporting surveys which are subject to both intentional and unintentional errors of recall by the respondent and therefore potentially inaccurate information. Due to the strong social stigma that alcohol drinking carries in many populations and denial by people with alcohol dependence, it is likely that many individuals underestimate and under-report their intake of alcohol, particularly in the case of heavy consumption. This would result in an underestimation of the actual carcinogenic effect of alcohol consumption. Thus, alcohol could be a stronger risk factor for cancer than indicated by published studies.

Key Findings

Review of alcohol consumption and risk of cancer

It is clear from a growing body of evidence that alcohol intake is associated with specific types of cancers. This indicates that particular organ systems may be more susceptible to alcohol-induced injury or that particular mechanisms may play a more critical role in specific tissues. Thus, it is important to recognise that the relationship between alcohol consumption and 'all cancers' may be heavily skewed by cancers at a limited number of sites. Therefore the results may not be generalisable to all cancers. According to published evidence from eight studies, moderate alcohol consumption corresponding to approximately two drinks of alcohol per day does not increase the risk of cancer in general. However, the average intake of approximately four drinks per day increases the risk of cancer by 22%. High alcohol consumption averaging approximately eight drinks per day increases the risk of cancer at any site by 90%.

Alcohol consumption and cancers of the upper aero-digestive tract

There is strong longstanding evidence that alcohol increases the risk of upper aero-digestive tract cancers, including cancers of the oral cavity, pharynx, oesophagus, and larynx. The evidence clearly shows that cancer risk increases with increasing alcohol consumption and there is no safety threshold or lower limit below which an effect is not evident. Alcohol intake averaging approximately two drinks per day increased the risk of cancer of the oral cavity and pharynx by approximately 75%, risk of cancer of the oesophagus by approximately 50%, and risk of cancer of the larynx by approximately 40%. When alcohol intake is doubled to an average of around four drinks per day, the risk of cancer of the oral cavity and pharynx, oesophagus, and larynx is more than twice that of a non-drinker. At high levels of alcohol consumption, around eight drinks per day, the risk of upper aero-digestive tract cancers is approximately 4-6 times that of a non-drinker. The increased risk of upper aero-digestive

tract cancers is also partially attributable to tobacco smoking. However, it is clear from studies of never-smokers that alcohol consumption also has an independent effect on risk.

More recent studies have provided further support for the strong association between alcohol consumption and risk of cancers of the upper aero-digestive tract. There is also some evidence that drinking alcoholic beverages outside meals increases the risk of developing particular cancers of the upper aero-digestive tract by 50-80% compared with those who drank with meals only.

Alcohol consumption and breast cancer

Intense research has been directed at understanding the relationship between breast cancer and the consumption of alcohol. In NSW, breast cancer accounts for approximately 27% of all cancers in women. Given its high incidence, even a small increase in the risk of breast cancer has serious public health implications with potentially large numbers affected.

A large body of evidence estimated the risk of breast cancer between 11 and 22% higher in women who drink alcohol compared with non-drinkers. For each additional alcoholic drink per day, the excess risk of breast cancer is approximately 10 to 12%. The increased risk associated with alcohol consumption is not influenced by menopausal status or nationality, and does not appear to differ with type of alcoholic beverage consumed.

Newer studies have provided further support for a positive association between alcohol intake and risk of breast cancer. Several studies showed a stronger association between alcohol consumption and breast cancer risk in postmenopausal women and also in women with oestrogen receptor-positive tumours. Further research is required to confirm these more recent findings.

A mounting body of evidence has indicated that low folate intake is also associated with elevated risk of several cancers, including breast cancer. Evidence to date indicates that modest intakes of folate may reduce the increased risks of breast cancer associated with alcohol consumption. However, recent evidence from a large European study of 274,688 women with 4,285 incident cases of invasive breast cancer appears contradictory and showed no interaction between alcohol intake and dietary folate. This same study showed that the increased risk of breast cancer associated with alcohol consumption was not different in users and non-users of hormone replacement therapy.

Alcohol consumption and colorectal cancer

Colorectal cancer is the second most common cancer in NSW, accounting for 13% of all cancers. Thus, even a moderate excess risk attributable to alcohol may also affect large numbers of people with important public health implications. Whilst there is no significant relationship between alcohol

consumption and risk of cancers of the colon and rectum in women, high alcohol intake in men is associated with a 64% increased risk of colon cancer and a 79% increased risk of rectal cancer. Increased risk of cancers of the colon and rectum was identified with alcohol consumption of only two drinks per week. Risk varied with geographical area of study participants for colon cancer but not cancer of the rectum.

Alcohol consumption and liver cancer

There is convincing evidence that heavy alcohol consumption increases the risk of primary liver cancer. The most probable mechanism is through the development of liver cirrhosis, although other pathways may also play a role. According to data from 20 studies, alcohol intake of approximately two drinks per day increases the risk of liver cancer by 17% compared with non-drinkers. Risk of liver cancer is increased by 36% with alcohol intake averaging four drinks per day. Heavy alcohol consumption such as eight drinks per day increased the risk of liver cancer by 86%. There is some evidence that risks are markedly higher in women. The risk of liver cancer in women with high alcohol intake is approximately nine-times that of non-drinkers whereas the risk in men is 1.6-times that in non-drinkers. However, data are limited and further studies are needed to confirm this apparent difference between the sexes.

Alcohol consumption and stomach cancer

Cancer of the stomach accounts for around 2% of all cancers in NSW and is more common in men. According to evidence from 16 studies, alcohol consumption is associated with a modest increase in risk of cancer of the stomach. Alcohol intake averaging two drinks per day increased the risk of stomach cancer by 7% compared with non-drinkers. Heavy alcohol intake of around eight drinks per day increased the risk of stomach cancer by 32% compared to non-drinkers.

Alcohol consumption and lung cancer

Lung cancer accounts for approximately 9% of all cancers in NSW. Although an association between alcohol drinking and lung cancer risk has been reported in the literature, the association is heavily confounded by tobacco smoking, to the extent that it is difficult to reliably determine any independent effect of alcohol consumption. The available evidence from 23 studies suggests there does not appear to be an association between moderate alcohol consumption and lung cancer. However, it is possible that high levels of alcohol intake of around six or more drinks per day increases the risk of lung cancer and this risk appears independent of risk from tobacco smoking. Further research is needed to exclude the possibility that alcohol consumption is an independent risk factor for lung cancer.

Alcohol consumption and prostate cancer

Prostate cancer is the most common cancer in NSW, accounting for 29% of all cancers in men. Several studies have found a positive association between alcohol intake and prostate cancer, while others have found no relationship. Evidence from 33 studies suggests there is no relationship between moderate alcohol intake and risk of prostate cancer. However, there is some evidence of an increased risk of up to 24% seen at higher levels of alcohol consumption of around four or more drinks per day. Further research is needed to exclude the possibility that heavy alcohol consumption is also a risk factor for prostate cancer.

Whilst several recent studies have reported an increased risk of prostate cancer with a particular type of alcoholic beverage, the type of beverage that provided the association is not consistent across these studies. One of the largest of the recent studies investigating the link between alcohol consumption and prostate cancer is a Melbourne study of 16,872 men who were followed-up from 1993 to the end of 2003. Overall, the Australian study provides no support for an association between alcohol consumption and risk of prostate cancer and no association between cancer risk and type of alcoholic beverage consumed.

Alcohol consumption and ovarian cancer

There is conflicting evidence in the literature for the association between alcohol consumption and risk of ovarian cancer with reports of an increased, decreased, and no change in risk. Data from 15 studies indicates that alcohol consumption does not increase the risk of ovarian cancer. However, the current evidence is not yet convincing and an association between alcohol intake and ovarian cancer cannot be ruled out.

Alcohol consumption and other cancers

A considerable body of evidence has shown that alcohol does not appear to be a risk factor for cancers of the pancreas, endometrium, and bladder. Likewise, the evidence does not support an association between alcohol consumption and risk of melanoma and cancers of small intestine, gallbladder, cervix, and kidney. However, data were available for only one or two studies for each of these cancer sites and therefore further research is needed to confirm these findings.

Although there is some evidence that alcohol consumption may be associated with a decreased risk of thyroid cancer, it is difficult to reliably interpret these results because of the associations between thyroid cancer, iodine intake, cigarette smoking and other factors.

There is some evidence from a pooled analysis that alcohol consumption decreases the risk of non-Hodgkin lymphoma. However, the studies included in the analysis were not identified systematically and therefore it is possible that the results may be biased.

Conclusions based on review of the evidence

Table 1 summarises the current state of evidence for the association between alcohol consumption and risk of cancer at specific sites. For many cancer sites where an association has been shown, there is a dose-response relationship with alcohol consumption that persists after adjustment for other potential confounding factors such as age and tobacco, for both men and women. There is no clear evidence of a threshold level below which alcohol intake is safe without the risk of cancer. Increased risks were often observed at alcohol intake classified by the NHMRC as responsible or low risk such as two alcoholic drinks per day. Unlike cardiovascular disease, there is no consistent evidence that alcohol intake at any level has a protective effect against cancer. There is no evidence to support that high risk alcohol consumption has any beneficial effects on health.

Table 1 Summary of evidence for a link between alcohol and cancer

Cancer site	Relationship between alcohol and cancer	Evidence base
Cancer at any site	No relationship with moderate consumption Increased risk with higher consumption	Convincing
Breast	Increased risk, even with moderate consumption	Convincing
Colon	Increased risk, even with moderate consumption	Convincing
Liver	Increased risk, even with moderate consumption	Convincing
Rectum	Increased risk, even with moderate consumption	Convincing
Stomach	Increased risk, even with moderate consumption	Convincing
Upper aero-digestive tract	Increased risk, even with moderate consumption	Convincing
Cervix	No relationship	Insufficient
Gallbladder	No relationship	Insufficient
Kidney	No relationship	Insufficient
Lung	Possibly increased risk, heavily confounded by smoking	Inconsistent
Melanoma	No relationship	Insufficient
Non-Hodgkin's lymphoma	Possibly decreased risk	Insufficient
Ovary	Conflicting – evidence of increased and decreased risk	Inconsistent
Prostate	No relationship with low consumption Possibly increased risk with heavy consumption	Inconsistent
Small intestine	No relationship	Insufficient
Thyroid	Possibly decreased risk, confounded by smoking	Inadequate
Bladder	No relationship	Convincing
Endometrium	No relationship	Convincing
Pancreas	No relationship	Convincing

NOTE: Moderate consumption is defined as up to 2 alcoholic drinks per day, which is classified as low risk according to 2001 NHMRC guidelines.

The AIHW estimated that excessive alcohol consumption may be responsible for 30-50% of all cancers of the upper-respiratory tract and over one-third of all liver cancers (**Table 41**; AIHW, 2006). Although the percentage of breast cancer cases attributable to excessive alcohol consumption is somewhat smaller at 12% (**Table 41**), this actually represents a large number of potentially preventable cases of breast cancer considering that breast cancer is the most common cancer in NSW women (Tracey *et al*, 2006).

Table 2 Cancer site and percentage of cancers attributed to excessive alcohol consumption

Cancers site	Males	Females
Oral cancers	39%	31%
Oesophagus	46%	40%
Larynx	51%	46%
Liver	39%	35%
Female breast cancer	-	12%

NOTE: Derived using aetiological fractions from Ridolfo & Stevenson, 2001
Source: Cancer in Australia: an overview, 2006. AIHW cat. No. CAN 32. Canberra: AIHW.

Alcohol attributable fractions are shown in **Table 42**. Only those cancer types with convincing evidence for a positive and significant association between alcohol intake and cancer risk are shown. In the population who consume an average of two alcoholic drinks per day (considered 'low risk' according to the 2007 draft NHMRC guidelines), it is estimated that alcohol is responsible for 43.2% of cancers of the oral cavity and pharynx, 30.1% of oesophageal cancers in men, 34.2% of oesophageal cancers in women, 22.5% of laryngeal cancers, 23.7% of female breast cancers, 7.4% of cancers of the colon and rectum, 14.5% of liver cancers, and 6.5% of cancers of the stomach.

Table 3 Alcohol attributable fractions for cancer by alcohol intake levels [a]

Cancers site	Alcohol intake		
	25 g/day	50 g/day	100 g/day
Any site	-	18.0%	47.6%
Oral cavity & pharynx [b]	43.2%	65.2%	83.6%
Oesophagus [c] – males	30.1%	49.5%	71.3%
– females	34.2%	55.4%	77.5%
Larynx [b]	22.5%	40.5%	64.2%
Breast	23.7%	40.1%	63.1%
Colon & rectum	7.4%	15.3%	27.5%
Liver	14.5%	26.5%	46.2%
Stomach	6.5%	13.0%	24.2%

[a] The RR estimates from Bagnardi *et al* (2001) were used to calculate the alcohol attributable fractions for men and women using the following formula (from NHMRC, 2007): AAFi = P × (RRi-1) / [P × (RRi-1) + 1], where i = level of drinking (ie, 25 g, 50 g, 100 g alcohol per day), P = 100% prevalence, assuming all drinkers drink in same quantity, RRi = relative risks for level i.
[b] Tobacco smoking-adjusted risk estimates are used for cancers of the oral cavity & pharynx, and larynx
[c] Risk estimates for oesophageal cancer are shown separately for men and women because of a significant gender effect ($P < 0.05$).

Conclusions

According to a report from the AIHW, in 2003 there were an estimated 2,844 new cases of cancer and 1,358 deaths from cancer in Australia attributed to excessive alcohol consumption. The age-standardised incidence rate for alcohol-attributed cancer was estimated to be 13.9 per 100,000 persons. The age-standardised mortality rate for alcohol-attributed cancer was estimated to be 6.6 per 100,000. These are likely to be underestimates because the association between alcohol consumption and cancers of the colon, rectum, and stomach were not considered in the calculations. Colorectal cancer is the second most common cancer in NSW with 4,517 new cases reported in 2004. Thus, even a modest

excess risk of colorectal cancer at low levels of alcohol consumption has serious public health implications given that almost 70% of individuals in NSW consume alcohol.

The AIHW estimated that excessive alcohol consumption may be responsible for 30-50% of all cancers of the upper-respiratory tract and over one-third of all liver cancers. Although the percentage of breast cancer cases attributable to excessive alcohol consumption is somewhat smaller at 12%, this actually represents a large number of potentially preventable cases of breast cancer considering that breast cancer is the most common cancer in NSW women.

In conclusion, alcohol is one of the most well established causes of cancer and causes a considerable burden of disease in terms of both mortality and morbidity. While the mechanisms of action of alcohol-related risks and benefits await further clarification, the overwhelming public health message is that high daily alcohol intake can have an adverse affect on health and for those who do drink alcohol, it is important to do so in moderation. While the total elimination of alcohol consumption is not realistic, there should be increased community awareness and understanding of the extent and impacts of 'risk drinking behaviour'.

A INTRODUCTION

A.1. BACKGROUND

Specific Australian data

Levels of alcohol intake

Levels of alcohol intake in the community are available from the *2006 Report on Adult Health from the New South Wales Population Health Survey*, which included questions on the consumption of alcohol. Overall, the survey found that 30.6% of adults do not drink alcohol, 51.9% were classified as low risk, 8.1% were classified as risky, and 9.5% were classified as high risk, according to the 2001 NHMRC Guidelines. The proportion of males reporting high risk alcohol drinking was significantly higher than the proportion of females (12.5% versus 6.5%, respectively). Just under one third of adults (32.8%) reported 'any risk drinking behaviour', defined as one or more of the following: consuming alcohol every day, consuming on average more than 4 if male or 2 if female 'standard drinks' per day, or consuming more than 6 if male or 4 if female 'standard drinks' on any one occasion in the past four weeks.

Encouragingly, the proportion of adults reporting any risk drinking behaviour decreased significantly between 1997 and 2006 in both men (50.6% in 1997 compared with 37.3% in 2006) and women (34.3% in 1997 compared with 28.4% in 2006).

Deaths and illness attributable to alcohol use

In Australia, alcohol is second only to tobacco as a cause of preventable morbidity and mortality. A 2007 publication from the Australian Institute of Health and Welfare (AIHW) reported that alcohol harm was responsible for 3.2% of the total burden of disease and injury in Australia in 2003. Alcohol abuse, road traffic accidents and suicide contributed two-thirds of the harm attributed to alcohol in 2003, whilst breast cancer and oesophageal cancer each contributed approximately 5% of the total alcohol-attributable burden. The association between alcohol consumption and risk of cancers of the colon, rectum, and stomach were not considered and therefore the estimate of harm attributed to alcohol may actually be an underestimate. According to the AIHW alcohol also prevented 0.9% per cent of the total burden, primarily through beneficial effects on ischaemic heart disease, stroke, and other unspecified conditions. Thus, the net impact of alcohol was to contribute to 2.3% of total health burden. In terms of deaths, alcohol was attributable for 2.6% of all deaths in Australia in 2003 but prevented 1.8% of all deaths. Thus the net impact of alcohol was to contribute to 0.8% of all deaths.

Previous Australian burden studies from the AIHW reported a substantially higher health benefit due to alcohol compared to the current study ie, an estimated 7,157 deaths being prevented in 1996 compared with only 2,346 deaths being prevented in 2003. This is due to the previous studies

underestimating the number of people who abstain from alcohol or drink less than 0.25 drinks per day. Importantly, the most recent AIHW report states that the protective effect of low alcohol intake on heart disease only becomes apparent after 45 years of age, whereas the harmful effects of alcohol are apparent at all ages. Furthermore, the benefits of alcohol consumption outweigh its harmful effects only in females over the age of 65.

According to the Report of the New South Wales Chief Health Officer, alcohol use caused an estimated 1,416 deaths in NSW in 2004 (1,021 males and 395 females). This represented 4.3% and 1.7% of all male and female deaths respectively in NSW. However, the age-adjusted rate of deaths attributable to alcohol has decreased in NSW by 36% between 1985 and 2004. In contrast, hospitalisations attributable to alcohol have risen by approximately 27% between 1989-90 and 2004-05. Alcohol was attributed to 2.5% and 1.2% of all male and female hospitalisations respectively in NSW in 2004. Again, these are likely to be underestimates because the association between alcohol and cancers of the colon, rectum, and stomach were not taken into consideration.

Mechanisms of alcohol carcinogenicity

The mechanisms by which alcoholic beverages exert their cancer-causing effect are not fully understood and are likely to differ depending on location within the body. There is strong evidence that the carcinogenic effect of alcoholic beverages is likely to be, at least for some cancer types, mediated by acetaldehyde, which is a highly toxic by-product of alcohol metabolism. Although the liver effectively clears acetaldehyde, the large intestine and saliva do not clear it as effectively and therefore acetaldehyde can build up to high levels in the gastrointestinal tract. Acetaldehyde interferes with DNA synthesis and repair which can consequently result in tumour development. Individuals with mutations in the genes responsible for the generation and detoxification of acetaldehyde have a markedly increased cancer risk, particularly for cancers of the upper aero-digestive tract.

There is also strong laboratory-based evidence that alcohol may impact upon cancer of the breast and ovary via its effects on oestrogen levels. Alcohol has been shown to increase oestrogen levels and increase oestrogen receptor activity, and also to down-regulate the expression of the breast cancer susceptibility gene BRCA1, which is a potent inhibitor of oestrogen receptor activity. This could promote cellular proliferation which may lead to tumour development.

In addition, a number of local mechanisms have been proposed. Alcoholic beverages may exert a carcinogenic effect by increasing the solubility of cancer-causing agents entering the lining of the oral cavity or perhaps by increasing the permeability of the lining of the oral cavity. This mechanism would explain the synergistic effect of tobacco smoking and alcohol drinking, whereby alcohol might serve as a solvent for the cancer-causing compounds in cigarette smoke and transport these chemicals to sites they otherwise would not reach.

Another possible mechanism is via the production of reactive oxygen species which can damage cells and DNA. It is proposed that chronic alcohol consumption can lead to increased generation of reactive oxygen species and increased conversion of various pre-cancerous compounds into cancer-causing agents.

There is also some evidence for a mechanism based on the relationship between excessive alcohol intake and impaired folate status, through decreased folate content of the diet, diminished intestinal absorption, and/or increased urinary excretion. Folate deficiency is linked to several cancers, including those of the cervix, lung, breast, and colo-rectum. Although the cellular pathways through which folate inadequacy promotes the likelihood of cancer are not fully understood, the most likely candidates are impairments in the critical role that folate plays in DNA synthesis and repair.

Other possible mechanisms include (i) an alcohol-induced deficiency in essential nutrients and dietary factors that are cancer protective, (ii) alcohol-induced alteration of the immune response, (iii) impurities and contaminants in alcoholic beverages that cause cancer, (iv) a direct toxic effect of highly concentrated alcoholic beverages on the epithelium, (v) alterations in the motility of the oesophagus and the cells that line the oesophagus due to alcohol, and (vi) a decrease in salivary flow leading to a decreased clearing of the lining of the gastrointestinal tract and accumulation of cancer-causing agents.

Interaction with tobacco

Alcohol consumption and tobacco smoking have been causally linked to cancers of the upper aero-digestive tract. However, separating the effects of alcohol and tobacco remains difficult since heavy drinkers tend to be heavy smokers and vice versa. Furthermore, many studies include very few participants who neither drink alcohol nor smoke tobacco. The effect of environmental exposure to tobacco could also be considered a potential source of confounding. In particular, non-smokers with high levels of alcohol consumption might have a heavier exposure to smoke if they drink in smoke-filled environments.

The combined effects of alcohol and smoking are greater than additive and are often multiplicative. Synergism between alcohol and tobacco was first reported in the 1970's and this synergistic effect has since been estimated to be attributable for over 75% of cancers of the upper aero-digestive tract in developed countries. One study showed that compared with the risk for non-smoking non-drinkers, the approximate relative risks for developing cancer of the oral cavity are seven times greater for those who use tobacco, six times greater for those who consume alcohol, and 38 times greater for those who use both tobacco and alcohol. Thus, despite the independent effect that alcohol has on the risk of upper aero-digestive tract cancers, it is the synergistic effect that causes the most harm.

Potential mechanisms for the multiplicative effect of alcohol and tobacco include the ability of alcohol to (i) act as a solvent for other carcinogens, and (ii) increase the permeability of oral mucosa to other

carcinogens. This would result in increased uptake of alcohol itself, and of carcinogens, with enhanced systemic effects. Furthermore, the enhanced penetration of carcinogens into proliferating cells may exert a direct mutagenic effect.

Differential effect of different types of alcoholic beverages

Analysis of cancer risk by type of alcoholic beverage has not provided consistent results. A few studies have shown a more protective effect from wine and a more harmful effect from beer and spirits. One difficulty in determining an independent effect of a particular alcohol type is that people who drink alcohol tend to drink a variety of alcohol-containing beverages. It is widely accepted that, in general, the beverage associated with the greatest risk of cancer is the most frequently consumed type of alcoholic beverage in each population, suggesting that no meaningful difference exists for different types of alcoholic beverages.

Other public health burdens associated with alcohol consumption

Alcohol dependence and excessive alcohol intake are associated with a number of physical and mental health problems that carry significant morbidity and mortality. Although a significant proportion of health problems and deaths are the result of the acute effects of excessive alcohol intake (eg, injuries and deaths due to alcohol-related driving accidents), many more can be attributed to the insidious effects of chronic, excessive consumption and alcohol dependence. In addition to an association with particular cancers, excessive alcohol consumption has direct adverse effects on the liver, nervous, and cardiovascular systems. Alcohol dependence is also associated with depression, psychiatric morbidity, and an increased risk of suicide. Furthermore, the children of women who consume alcohol while pregnant may be born with permanent disorders that affect mental health and growth.

Protective effect in heart disease

Although the risk of cancer, cirrhosis of the liver, and alcohol dependence all rise with increasing daily alcohol intake, there is a considerable body of evidence that shows a reduction in the risk of harm with low levels of alcohol consumption, due to a specific reduction of ischaemic heart disease and stroke events. Based on epidemiologic evidence, a J-shaped relationship is seen for alcohol consumption and risk of coronary heart disease, whereby low to moderate average consumption of alcohol appears to confer a lower risk of coronary heart disease incidence and mortality compared to abstinence, whereas heavy average consumption is associated with a risk higher than that for non-drinkers.

However, the J-shaped relationship between alcohol and health benefits has been questioned in more recent publications. It has been suggested that the older studies may have overestimated the health benefits of alcohol consumption by classifying people who have recently stopped or reduced their drinking as 'abstainers', since those who have recently reduced or stopped drinking alcohol may have done so because of alcohol-related ill health.

A recent Melbourne study investigated the relationship between alcohol intake and mortality due to coronary heart disease and cardiovascular disease and found that usual daily alcohol intake was associated with a reduction in death due to coronary heart disease and cardiovascular disease in women. Moreover, increased drinking frequency actually decreased death due to coronary heart disease and cardiovascular disease in men. Another recent study investigated the relationship between alcohol consumption and risk of death according to age and gender and found a direct dose-response relation between alcohol consumption and risk of death in men aged 16-34 years and women aged 16-54 years. Taken together, the body of evidence suggests that levels of alcohol consumption of the order of one drink per two days may be cardioprotective, but only in older individuals – men over 45 years of age and women after menopause. However, the evidence does not support that people should specifically take up or maintain drinking to obtain health benefits.

A.2. IARC CLASSIFICATION

In 1988, the World Health Organization (WHO) International Agency for Research on Cancer (IARC) classed alcohol as a Group 1 carcinogen, which is the highest IARC classification in humans (IARC, 1988). Its evaluation states: *"There is sufficient evidence for the carcinogenicity of alcoholic beverages in humans. The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver is causally related to the consumption of alcoholic beverages. Alcoholic beverages are carcinogenic to humans (Group 1).*"

The carcinogenicity of alcoholic beverages was reassessed by IARC in February 2007 (IARC, 2007) and a summary of the data and evaluation is available on the IARC Monograph's programme website [10]. The Working Group concluded: *"There is sufficient evidence in humans for the carcinogenicity of alcoholic beverages. The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colo-rectum and female breast is causally related to the consumption of alcoholic beverages. There is evidence suggesting lack of carcinogenicity in humans for alcoholic beverages and cancer of the kidney and non-Hodgkin lymphoma. There is substantial mechanistic evidence in humans who are deficient in aldehyde dehydrogenase that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to the causation of malignant oesophageal tumours."*

The overall evaluation states:

> Alcoholic beverages are *carcinogenic to humans (Group 1).*
>
> Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1).*

A.3. AUSTRALIAN GUIDELINES

A.3.1. The National Health and Medical Research Council (NHMRC)

[10] Available at http://monographs.iarc.fr/ENG/Meetings/96-alcohol.pdf [last accessed 17 October 2007]

The key national guidelines that outline recommendations in relation to alcohol consumption *Australian alcohol guidelines: health risks and benefits* were published by the NHMRC in 2001 and are currently under review. It is important to recognise that this guidance relates to all health risks and benefits associated with alcohol consumption, not just cancer. These guidelines state that to minimise risks in the short and longer term, and gain any longer-term benefits:

- Men should drink an average of no more than four standard drinks a day; not more than 6 standard drinks in any one day; no more than twenty-eight standard drinks per week, and have one or two alcohol-free days per week.

  Women should drink an average of no more than two standard drinks a day; not more than 4 standard drinks in any one day; no more than fourteen standard drinks per week, and have one or two alcohol-free days per week. [Note: A standard drink is defined as containing 10 g of alcohol]

The 2001 guidelines specified two levels of drinking above guideline levels, designated as 'risky' and 'high risk' (see **Table 2** for definitions)[11]. The 2001 guidelines have been used as the basis for the National Alcohol Strategy 2006-2009, which was endorsed by the Ministerial Council on Drug Strategy in May 2006. The strategy outlines priority areas for coordinated action to develop drinking cultures that support a reduction in alcohol-related harm in Australia.

Table 2 Risk associated with alcohol consumption: NHMRC 2001

For risk of harm in the short-term (standard drinks):				For risk of harm in the long-term (standard drinks):			
	Low risk	**Risky**	**High risk**		**Low risk**	**Risky**	**High risk**
Males							
on any one day	Up to 6 No more than 3 days per week	7 to 10	11 or more	on an average day Overall weekly level	Up to 4 per day Up to 28 per week	5 to 6 per day 29 to 42 per week	7 or more per day 43 or more per week
Females							
on any one day	Up to 4 No more than 3 days per week	5 to 6	7 or more	on an average day Overall weekly level	Up to 2 per day Up to 14 per week	3 to 4 per day 15 to 18 per week	5 or more per day 29 or more per week

Note 1: It is assumed that the drinks are consumed at a moderate rate to minimise intoxication, eg, for men no more than 2 drinks in the first hour and 1 per hour thereafter, and for women, no more than 1 drink per hour.
Note 2: These guidelines apply to persons of average or larger size, ie, above about 60 kg for men and 50 kg for women. Persons of smaller than average body size should drink within lower levels.

[11] The table provided in the 2001 NHMRC guidelines is based upon International Guide for Monitoring Alcohol Consumption and Related Harm, WHO, Geneva, 2000.

The more recent 2003 NHMRC *Dietary guidelines for Australian adults* set a lower recommended level of alcohol consumption based on the energy density of alcohol contributing to weight problems (NHMRC, 2003). The dietary guidelines advise adults:

- Limit your alcohol intake if you choose to drink.
- Because of alcohol's effect on both short- and long-term health, and because of the additional kilojoules it provides in the diets of a society with increasing rates of obesity, adults - if they drink at all - should limit their average daily intake of alcohol to no more than two standard drinks a day for men and one standard drink a day for women.

In October 2007 a draft of *Australian alcohol guidelines for low-risk drinking* was released by the NHMRC for public consultation. The draft guidance has changed significantly since the 2001 edition and is more aligned with the 2003 Dietary Guidelines. The NHMRC has now specified a simplified, universal guideline level for alcohol intake for both immediate and long-term risks (Guideline 1), which is significantly lower than the 2001 guideline levels. The guidelines for children, and for women during pregnancy and breastfeeding, are both more conservative than the 2001 guidelines, with advice to consider not drinking in these situations. The updated guidelines no longer specify 'risky' and 'high risk' drinking levels, but take the position that risk increases progressively with the amount of alcohol consumed and thus any drinking above the guideline levels carries a higher risk than not drinking (p18 of the Draft for Public Consultation, 2007).

The guidelines proposed in the 2007 Draft for Public Consultation (p11) are as follows:

Guideline 1: For low risk of both immediate and long-term harm from drinking

- Men and women, two standard drinks or less in any one day

Guideline 2: For children and young people under 18 years of age

- Parents and carers are advised that not drinking is the safest option for children and adolescents under 15 years of age
- Not drinking is the safest option for adolescents aged 15-17 years. If drinking does occur, it should be under parental supervision and within the adult Guideline for low-risk drinking (two standard drinks or less in any one day)

Guideline 3: For women who are pregnant, are planning a pregnancy or are breast feeding

- Not drinking is the safest option

The draft guidelines provide additional health advice and precautions for:

- Situations where not drinking is the safest option (ie, taking part in, or supervising, risky activities; using illicit drugs),
- People who should be aware that they are at increased risk if they drink (ie, young adults; older people; people with a family history of alcohol dependence)
- People who should seek health professional advice if they are considering drinking (ie, people with a physical condition made worse by alcohol; people with a mental health problem made worse by alcohol; people taking medications)

The 2007 draft guidelines provide the following rationale for Guideline 1 (p39): *This guideline applies to men and women aged 18 years or over and sets a standard drinking level that will reduce both the risk of injury, violence and self harm, and the risk of developing alcohol-related diseases. The guideline limits are based on international epidemiological research that has quantified the risks of injuries and alcohol-related diseases after different levels of alcohol consumption (converted to Australian drinks) and with different patterns of drinking. Importantly, this guideline does not represent a 'safe' or 'no-risk' drinking level; neither is it a prescribed intake level. Rather, it represents a drinking level that, for healthy adults, will:*

- *Keep the risk of accidents and injuries, or of developing alcohol-related diseases, at tolerably low levels (compared with not drinking)*
- *Reduce the lifetime risk of death from an alcohol-related injury or disease to less than 1 in 100 people who drink at that level*

The analysis which was undertaken to derive a 'low-risk' drinking level in adults was based primarily on data from a 1999 systematic review and meta-analysis reported by Corrao and colleagues (see **Appendix 4** for further details of this study). In terms of alcohol-related diseases, a range of chronic conditions were included where accepted epidemiological criteria have shown a causal and detrimental effect of alcohol consumption. The analysis incorporated risks of developing the following conditions: lip, oral and pharyngeal cancer; oesophageal cancer; liver cancer; breast cancer; hypertensive disease; ischaemic heart disease; ischaemic stroke; haemorrhagic stroke; cirrhosis of the liver; and alcohol use disorders.

The NHMRC acknowledge the controversial body of evidence regarding an apparent reduction in the risk of harm with low levels of alcohol consumption (see **Section D.2**), however state that *"Any risk reduction needs to be balanced against the risks of contracting cancer or other chronic diseases at low levels of drinking"* (p16).

With respect to cancer, the draft guidelines state *"alcohol is associated with an increased risk of cancer overall, and is a cause of cancer of the mouth, throat and oesophagus. Alcohol is also a risk factor for other cancers, such as cancer of the stomach, breast, liver and pancreas, and has also been associated with bowel cancer"* (p29).

A.3.2. The Cancer Council Australia

According to The Cancer Council Australia National Cancer Prevention Policy 2004-2006, The Cancer Council supports the lower recommendations for alcohol specified in the NHMRC *Dietary guidelines for Australian adults*, as drinking at these levels is both more appropriate for preventing obesity and decreasing the risk of all-cause mortality and cancer. The Cancer Council recommends that, to reduce the risk of cancer, alcohol consumption should be limited or avoided.

The Cancer Council Australia advises[12] that if you choose to drink:

- Limit your intake
- Avoid binge drinking
- Have at least 1-2 alcohol-free days every week
- Choose low-alcohol drinks
- Eat some food when you drink.

A.3.3. The National Heart Foundation of Australia

The National Heart Foundation of Australia states the following[13]:

- One or two standard drinks per day may do you no harm (assuming you are a reasonably healthy adult), but excessive drinking of alcohol increases your risk of high blood pressure, heart disease and stroke, as well as many other problems. Alcohol does not raise blood cholesterol, but it can raise triglycerides, blood pressure and body weight.

The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand 2007 *Guidelines for preventing cardiovascular events in people with coronary heart disease* states the following in relation to alcohol[14]:

- GOAL: Low risk alcohol consumption

[12] *Source:* Alcohol and Cancer fact sheet, available at http://www.cancer.org.au//File/Cancersmartlifestyle/Alcoholandcancerprevention.pdf

[13] *Source:* http://www.heartfoundation.org.au/Healthy_Living/Eating_and_Drinking/Drinks.htm

[14] *Source:* http://www.heartfoundation.org.au/document/NHF/reducingrisk_heartdisease_summary_2007.pdf

- Encourage patients with hypertension who drink alcohol to limit intake to no more than 2 standard drinks per day (men), or 1 standard drink per day (women).
- It is not recommended that abstainers should take up drinking or that drinkers should increase their alcohol intake.

In a clinical practice *Consensus statement for the prevention of vascular disease* produced by The National Vascular Disease Prevention Alliance on behalf of the National Heart Foundation of Australia, Diabetes Australia, Kidney Health Australia, and National Stroke Foundation of Australia, the following treatment target is proposed[15]:

- Low risk drinking pattern
- For those with hypertension: ≤2 standard drinks per day for men, and ≤1 standard drinks per day for women.

A.4. INTERNATIONAL GUIDELINES

In 2003, the World Health Organization (WHO) made the following recommendation regarding alcohol consumption [16]:

- Consumption of alcoholic beverages is not recommended: if consumed, do not exceed two units per day. (One unit is equivalent to approximately 10 g of alcohol and is provided by one glass of beer, wine or spirits)

The International Center for Alcohol Policies (ICAP) has produced a table of sensible drinking guidelines from various countries. The table includes the entity that developed the guidelines, recommendations for men and women, size of the standard drink in grams of ethanol, and other recommendations or notes. The table was last updated February 2007 and can be accessed at the following address:
http://www.icap.org/PolicyIssues/DrinkingGuidelines/GuidelinesTable/tabid/204/Default.aspx

A modified version of the table is presented in **Appendix 1**, supplemented with additional information relevant to alcohol and cancer risk. This additional information is shown in grey text.

[15] *Source:* http://www.heartfoundation.org.au/document/NHF/nvdpa_04.pdf

[16] In *Diet Nutrition and the prevention of chronic diseases.* Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series 916. 2003. World Health Organization: Geneva.

B REVIEW OF EXISTING SYSTEMATIC REVIEWS AND META-ANALYSES

The aim of the current literature review was to provide a summary of the evidence relating to the relationship between alcohol consumption and cancer. A suitable existing systematic review was sought for specific cancer types, rather than cancer in general as alcohol consumption is likely to impact differentially upon each tissue. The findings of each key review were considered in detail, followed by a brief review of subsequent original papers.

B.1. LITERATURE SEARCH FOR SYSTEMATIC REVIEWS

B.1.1. Search strategy

Full details of the search strategy are presented in **Appendix 2**. The aim of the search strategy was to identify published systematic reviews or meta-analyses of alcohol consumption associated with risk of cancer. Narrative reviews were excluded. Medline and EMBASE were searched using EMBASE.com, with the Cochrane Library (including DARE) searched separately. Citations and abstracts were downloaded into *Reference Manager Version 10*, and duplicate citations were removed. Following examination of the abstracts and descriptors, all potentially relevant papers were retrieved.

Manual searching of the bibliographies of the retrieved papers was undertaken to identify any additional publications not found in the electronic search. Four publications were considered for inclusion based on manual searching. Three of these papers were ultimately excluded following the retrieval of the full publication (see **Appendix 2**, Table 43). A report published by the Australian Institute of Health and Welfare (Ridolfo & Stevenson, 2001) contains a systematic review of alcohol and breast cancer, and was therefore included.

B.1.2. Selection of relevant publications

To be included in the current review, the literature search conducted in the identified systematic reviews must have included terms for cancer and/or alcohol, but not other search terms (eg, tobacco or diet) which would have limited the search results to an extent that was too narrow for the purpose of this analysis. Furthermore, identified systematic reviews must have contained sufficient details to indicate that some sort of systematic literature search was undertaken to identify individual studies. At the very least, a search of Medline was mandatory to indicate that publications were identified through a systematic process. In some cases, the authors referred to methodology reported in a previous publication, which was acceptable as long as the literature search in the previous publication referred to Medline. The quality of the reporting of the literature search was found to be highly variable, often with limited (or absent) details of the specific search terms and date range of the search, particularly in

the older publications. Meta-analyses that were reported without details of a literature search were excluded on the basis that there may have been preferential selection of the included studies or unintentional omission of other relevant published data.

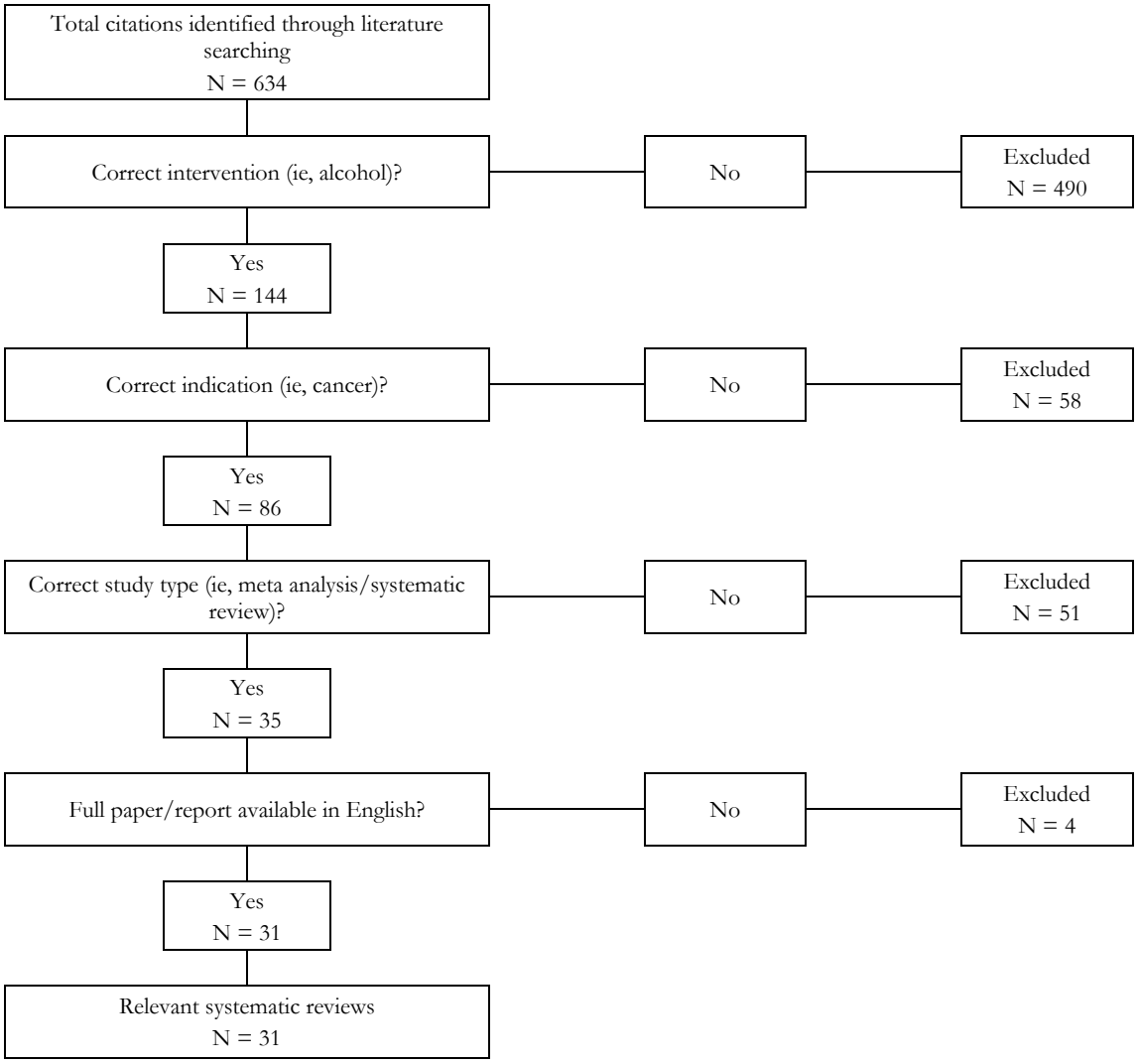
Reasons for exclusion are presented in **Appendix 3**. However, for clarity some examples of reasons for exclusion are discussed in more detail here. A number of full publications were reviewed but subsequently excluded on the basis that studies were pooled, without evidence of a systematic literature search. The studies involved in the respective analyses were not found by a database search; rather, they were selected on the basis of, for example, having been conducted in the authors' country/region of origin, or having been identified through a literature search for a related topic (eg, cancer and diet). These studies were excluded on the basis of being the wrong study type (ie, not a genuine systematic review). (See **Appendix 2,** Table 45.)

A group of publications pertaining to the 'Pooling Project of Prospective Studies of Diet and Cancer', which is an international consortium of cohort studies with the goal of analysing diet and cancer associations using standardised criteria across studies. Although the publications are relevant to alcohol and cancer research, the studies included in each review were identified as part of a project involving the compulsory collection of data on many dietary factors, which would have limited the search results for the purpose of this analysis. These studies were excluded on the basis of having the wrong intervention (ie, diet including alcohol, rather than any alcohol data). (See **Appendix 2,** Table 46).

Six studies examined the association between polymorphisms (eg, aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH), cytochrome P450 2E1 5'-flanking region (*CYP2E1PstI/RsaI*)) and cancer. The use of polymorphisms as surrogates for measuring exposure levels allows the assessment of the causal nature of alcohol exposure. These studies were excluded on the basis of having the wrong intervention (ie, presence of specific genotypes rather than the consumption of alcohol *per se*). (See **Appendix 2,** Table 47).

The final results of the application of these criteria to the results of the literature search are presented in **Figure 1**. Of the 634 citations identified, 31 relevant systematic reviews were identified. The other publications either did not involve or search for the correct intervention ie, alcohol; did not involve the correct indication ie, cancer; were not the correct study type ie, genuine and complete systematic review; or did not have the full publication available in English. Note that the latter is a potential source of bias. Publications may have had more than one reason for exclusion, but were excluded according to the hierarchy shown in **Figure 1**.

Figure 1 Flowchart showing exclusion of citations



B.1.3. Selection of key and supporting reviews

The citations for all 31 relevant publications which met the search criteria are listed in **Table 3**, categorised according to cancer type and listed in order of publication date. A review of each of the 31 publications is provided in **Appendix 4**.

Table 3 Relevant publications by cancer type and publication date

MULTIPLE CANCER SITES
Burger M, Bronstrup A, and Pietrzik K. (2004) Derivation of tolerable upper alcohol intake levels in Germany: A systematic review of risks and benefits of moderate alcohol consumption. Preventive Medicine 39:111-127.
Corrao G, Bagnardi V, Zambon A, and La Vecchia C. (2004) A meta-analysis of alcohol consumption and the risk of 15 diseases. Preventive Medicine 38:613-619.
Bagnardi V, Blangiardo M, La Vecchia C, and Corrao G. (2001) A meta-analysis of alcohol drinking and cancer risk. British Journal of Cancer 85:1700-1705.
Bagnardi V, Blangiardo M, La Vecchia C, and Corrao G. (2001) Alcohol consumption and the risk of cancer: a meta-analysis. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse and Alcoholism 25:263-270.

Gutjahr E and Gmel G. (2001) Defining alcohol-related fatal medical conditions for social-cost studies in Western societies: An update of the epidemiological evidence. Journal of Substance Abuse 13:239-264.

Corrao G, Bagnardi V, Zambon A, and Arico S. (1999) Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: A meta-analysis. Addiction 94:1551-1573.

Holman CDJ, English DR, Milne E, and Winter MG. (1996) Meta-analysis of alcohol and all-cause mortality: A validation of NHMRC recommendations. Medical Journal of Australia 164:141-145.

Burzynski NJ, Yancey JM, Fletcher DR, and Flynn MB. (1995) The carcinogenic risks of alcoholic beverages: Implications for cancer education. Journal of Cancer Education 10:34-36.

Anderson P, Cremona A, Paton A, Turner C, and Wallace P. (1993) The risk of alcohol. Addiction 88:1493-1508.

BREAST CANCER

Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, Davies DS, and Elliott P. (2006) Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes and Control 17:759-770.

Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, and Sherman ME. (2004) Etiology of hormone receptor-defined breast cancer: A systematic review of the literature. Cancer Epidemiology Biomarkers and Prevention 13:1558-1568.

Shi JQ and Copas JB. (2004) Meta-analysis for trend estimation. Statistics in Medicine 23:3-19.

Okasha M, McCarron P, Gunnell D, and Davey Smith G. (2003) Exposures in childhood, adolescence and early adulthood and breast cancer risk: A systematic review of the literature. Breast Cancer Research and Treatment 78:223-276.

Ellison RC, Zhang Y, McLennan CE, and Rothman KJ. (2001) Exploring the relation of alcohol consumption to risk of breast cancer. American Journal of Epidemiology 154:740-747.

Ridolfo,B and C Stevenson. The quantification of drug-caused mortality and morbidity in Australia, 1998. 2001. Canberra, Australian Institute of Health and Welfare (Report).

Tseng M, Weinberg CR, Umbach DM, and Longnecker MP. (1999) Calculation of population attributable risk for alcohol and breast cancer (United States). Cancer Causes and Control 10:119-123.

Longnecker MP. (1994) Alcoholic beverage consumption in relation to risk of breast cancer: Meta-analysis and review. Cancer Causes and Control 5:73-82.

Roth HD, Levy PS, Shi L, and Post E. (1994) Alcoholic beverages and breast cancer: Some observations on published case-control studies. Journal of Clinical Epidemiology 47:207-216.

Greenland S and Longnecker MP. (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American Journal of Epidemiology 135:1301-1309.

Longnecker MP, Berlin JA, Orza MJ, and Chalmers TC. (1988) A meta-analysis of alcohol consumption in relation to risk of breast cancer. Journal of the American Medical Association 260:652-656.

CANCER OF THE COLON AND RECTUM

Moskal A, Norat T, Ferrari P, and Riboli E. (2006) Alcohol intake and colorectal cancer risk: A dose-response meta-analysis of published cohort studies. International Journal of Cancer 120:664-671.

Herbey II, Ivankova NV, Katkoori VR, and Mamaeva OA. (2005) Colorectal cancer and hypercholesterolemia: Review of current research. Experimental Oncology 27:166-178.

Longnecker MP, Orza MJ, Adams ME, Vioque J, and Chalmers TC. (1990) A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes & Control : CCC 1:59-68.

LIVER CANCER

Donato F, Gelatti U, Limina RM, and Fattovich G. (2006) Southern Europe as an example of interaction between various environmental factors: A systematic review of the epidemiologic evidence. Oncogene 25:3756-3770.

LUNG CANCER

Korte JE, Brennan P, Henley SJ, and Boffetta P. (2002) Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. American Journal of Epidemiology 155:496-506.

PROSTATE CANCER

Dennis LK. (2000) Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. Prostate 42:56-66.

OVARIAN CANCER

Webb PM, Purdie DM, Bain CJ, and Green AC. Alcohol, wine, and risk of epithelial ovarian cancer . Cancer Epidemiology Biomarkers and Prevention 2004; 13: 592-599.

URINARY TRACT/BLADDER CANCER
Zeegers MPA, Tan FES, Verhagen AP, Weijenberg MP, and van den Brandt PA. (1999) Elevated risk of cancer of the urinary tract for alcohol drinkers: A meta-analysis. Cancer Causes and Control 10:445-451.
Zeegers MP, Kellen E, Buntinx F, and van den Brandt PA. (2004) The association between smoking, beverage consumption, diet and bladder cancer: a systematic literature review. World Journal of Urology 21:392-401.
KIDNEY CANCER (RENAL CELL CARCINOMA)
Dhote R, Pellicer-Coeuret M, Thiounn N, Debre B, and Vidal-Trecan G. (2000) Risk factors for adult renal cell carcinoma: A systematic review and implications for prevention. BJU International 86:20-27.
THYROID CANCER
Mack WJ, Preston-Martin S, Dal Maso L, Galanti R, Xiang M, Franceschi S, Hallquist A, Jin F, Kolonel L, La Vecchia C, Levi F, Linos A, Lund E, McTiernan A, Mabuchi K, Negri E, Wingren G, and Ron E. (2003) A pooled analysis of case-control studies of thyroid cancer: Cigarette smoking and consumption of alcohol, coffee, and tea. Cancer Causes and Control 14:773-785.

Table 4 summarises the cancer types studied in each of the systematic reviews. The association between alcohol consumption and risk of upper aero-digestive tract cancers was studied in eight publications, breast cancer in 20 studies, colon/rectal cancer in 10 studies, liver cancer in seven studies, pancreatic cancer in four studies, lung cancer in five studies, prostate cancer in three studies, ovarian cancer in four studies, and other cancer types in eight studies.

Key systematic reviews and meta-analyses were selected for each cancer type, based on currency, study quality, and comprehensiveness in terms of the number of included studies and the extent of the analyses conducted. For several cancer types, additional reviews were used to corroborate the findings of the key studies. The study reported by Bagnardi *et al* (2001a) and Corrao *et al* (2004) were often used as supportive evidence because they examined the risk of cancer at multiple sites. Where no superior evidence was available for a particular cancer type, these studies of multiple cancer sites were selected as the key review. In such cases, the scope of the analyses undertaken to assess the relationship between alcohol and cancer risk and to examine possible sources of bias and confounding was comparatively limited. Key and supportive studies for each type of cancer are listed in **Table 5**. Brief reasons for non-selection are listed in **Table 6**.

Table 4 Summary of the type of cancer studied in each of the identified systematic reviews, by year of publication

Study by year of publication	Upper aero-digestive tract	Breast	Colon, rectum	Liver	Pancreas	Lung	Prostate	Ovary	Other types
Donato *et al*, 2006				✓					
Key *et al*, 2006		✓							
Moskal *et al*, 2006			✓						
Herbey *et al*, 2005			✓						
Althuis *et al*, 2004		✓							
Burger *et al*, 2004	✓	✓	✓						
Corrao *et al*, 2004	✓	✓	✓	✓					
Shi and Copas, 2004		✓							
Zeegers *et al*, 2004									✓
Mack *et al*, 2003									✓
Okasha *et al*, 2003		✓							
Korte *et al*, 2002						✓			
Bagnardi *et al*, 2001a	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bagnardi *et al*, 2001b	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ellison *et al*, 2001		✓							
Gutjahr *et al*, 2001	✓	✓	✓	✓	✓	✓		✓	✓
Ridolfo & Stevenson, 2001		✓							
Webb *et al*, 2001								✓	
Dennis *et al*, 2000							✓		
Dhote *et al*, 2000									✓
Corrao *et al*, 1999	✓	✓	✓	✓					
Tseng *et al*, 1999		✓							
Zeegers *et al*, 1999									✓
Holman *et al*, 1996	✓	✓		✓					
Burzynski *et al*, 1995		✓							
Longnecker *et al*, 1994		✓							
Roth *et al*, 1994		✓							
Anderson *et al*, 1993	✓	✓	✓		✓	✓		✓	✓
Greenland & Longnecker, 1992		✓							
Longnecker *et al*, 1990			✓						
Longnecker *et al*, 1988		✓							

Table 5 Key and supportive systematic reviews by cancer type

Cancer type	Key systematic review	Supportive systematic review
Cancer at any site	Bagnardi *et al*, 2001a	-
Upper aero-digestive tract	Bagnardi *et al*, 2001a	Corrao *et al*, 2004
Breast	Key *et al*, 2006	Bagnardi *et al*, 2001a Corrao *et al*, 2004 Ridolfo & Stevenson, 2001
Colon/rectum	Moskal *et al*, 2006	Bagnardi *et al*, 2001a Corrao *et al*, 2004
Liver	Bagnardi *et al*, 2001a	Corrao *et al*, 2004
Pancreas	Bagnardi *et al*, 2001a	-
Lung	Korte *et al*, 2002	Bagnardi *et al*, 2001a
Prostate	Dennis *et al*, 2000	Bagnardi *et al*, 2001a
Ovary	Webb *et al*, 2001	Bagnardi *et al*, 2001a
Stomach	Bagnardi *et al*, 2001a	-
Other cancers	Bagnardi *et al*, 2001a	-

Table 6 Reasons for non-selection of systematic reviews, by year of publication

Study	Dates covered by literature search	Selection as key or supportive review	Comment/reason for non-selection
Donato *et al*, 2006	1989-Dec 2005	×	Selected studies in Southern Europe. Descriptive reporting of findings. Meta-analysis not conducted.
Key *et al*, 2006	Jan 1966-Dec 2003	✓	Comprehensive analysis of alcohol and breast cancer risk with appropriate sensitivity analyses.
Moskal *et al*, 2006	1990-2005	✓	Cohort studies only. Most comprehensive analysis of alcohol and risk of cancer of colon/rectum.
Herbey *et al*, 2005	1990-2005	×	Study of various risk factors. Descriptive reporting of findings. Relative risks not reported. Meta-analysis not conducted.
Althuis *et al*, 2004	1966-2004	×	Alcohol intake not a major focus. Descriptive reporting of findings. Meta-analysis not conducted.
Burger *et al*, 2004	1988-1999	×	Included studies used to derive tolerable upper alcohol intake levels for the German adult population. Relative risks not reported. Meta-analysis not conducted.
Corrao *et al*, 2004	1966-1998	✓	Methodology similar to Bagnardi *et al* (2001a) but with fewer studies due to stricter selection criteria.
Shi & Copas, 2004	Not conducted	×	Uses the effect of alcohol on the risk of breast cancer to illustrate statistical methodology. Re-analysis of Longnecker *et al* (1988) and Greenland & Longnecker (1992).
Zeegers *et al*, 2004	1966-August 2003	×	Refers to previous study from the same authors without identification of any other studies. Descriptive reporting of findings only.
Mack *et al*, 2003	1980-1997	×	Crude analysis only of beer and wine consumption
Okasha *et al*, 2003	1966-2002	×	Alcohol use not a major focus. Investigates impact of various pre-adult exposures Descriptive reporting of findings. Meta-analysis not conducted.
Korte *et al*, 2002	not specified [a]	✓	Comprehensive analysis of alcohol and risk of lung cancer, with appropriate adjustment for smoking.
Bagnardi *et al*, 2001a	1966-2000	✓	Includes multiple cancer types.
Bagnardi *et al*, 2001b	1966-2000	×	Duplicate data from Bagnardi *et al*, 2001a with marginally different results. Reports incidence but not mortality.

Study	Dates covered by literature search	Selection as key or supportive review	Comment/reason for non-selection
Ellison *et al*, 2001	1966-Oct 1999	×	Publication by Key *et al* (2006) is more current and comprehensive.
Gutjahr *et al*, 2001	Not stated	×	Update of English *et al*, 1995. Descriptive reporting of findings. Relative risks not reported.
Ridolfo & Stevenson, 2001	1988-1998	✓	Update of English *et al*, 1995. Used as supportive evidence for alcohol and risk of breast cancer.
Webb *et al*, 2001	1966-2003	✓	Australian study. Reports case-control study which is meta-analysed with other studies identified in a systematic literature search
Dennis *et al*, 2000	1976-July 1998	✓	Most comprehensive analysis of alcohol and risk of prostate cancer.
Dhote *et al*, 2000	1987-1998	×	Study of various risk factors. Descriptive reporting of findings. Meta-analysis not conducted.
Corrao *et al*, 1999	1966 through 1998	×	Superseded by Bagnardi *et al* (2001) and Corrao *et al* (2004)
Tseng *et al*, 1999	Not conducted	×	Not original meta-analysis. Estimates population attributable risk based on previously published meta-analysis, SEER statistics and general population data.
Zeegers *et al*, 1999	To April 1999	×	No dose-response relationship shown even though this was reported in primary studies.
Holman *et al*, 1996	1987 to end of 1993	×	Literature search conducted to update Holman *et al*, 1990. Not current.
Burzynski *et al*, 1995	conducted in 1992	×	Very limited details and results reported.
Longnecker *et al*, 1994	1966-1992	×	Seminal review and meta-analysis, but not current.
Roth *et al*, 1994	from 1980	×	Does not include cohort studies. Not current.
Anderson *et al*, 1993	Dates not provided	×	Reports incidence (RR) graphically. Not current.
Greenland & Longnecker, 1992	Not conducted	×	Methodological update of Longnecker *et al*, 1988, but superseded by Longnecker *et al*, 1994.
Longnecker *et al*, 1990	1966-1989	×	Not current.
Longnecker *et al*, 1988	1966-1987	×	Superseded by Longnecker *et al*, 1994

[a] Although the dates of the literature search were not provided, the analysis included studies from 1967 to 1999.

The eight key and supportive publications are reviewed in detail in **Appendix 4**, including an assessment of quality according to NHMRC criteria. **Section B.3** presents the outcomes from these publications in terms of cancer risk associated with alcohol consumption, by cancer type. The remaining 23 publications (not selected as key or supportive reviews) are reviewed in brief in **Appendix 4**.

The current review of the evidence for alcohol consumption and cancer risk was not limited entirely to the studies listed above. For specific cancer types where there is convincing evidence for a known confounder (eg, tobacco and cancers of the upper aero-digestive tract cancers) or a growing body of evidence for a risk modifier (eg, folate and breast cancer), additional supportive evidence was obtained from systematic reviews focussing specifically on these issues.

B.2. LITERATURE SEARCH FOR PIVOTAL NEW STUDIES

A literature search was conducted to identify any pivotal new studies published since the key systematic reviews for each of the specific cancer types specified within the scope of the current review. The search strategy is documented in **Appendix 5**.

All 1,149 citations and abstracts (where available) were downloaded into *Reference Manager Version 10* and their content reviewed to identify any primary studies published since the key and supportive meta-analyses listed in **Table 5**. For each cancer type, these newer studies were tabulated with a brief description of the study type, country where the study took place, study size, and conclusion regarding the association between alcohol consumption and cancer risk. These tables appear after the discussion of the key and supportive systematic reviews for each cancer type in **Sections B.3.2** to **B.3.11**, and the general findings from the newer studies are discussed in light of the findings from the key systematic reviews.

B.3. REVIEW OF ALCOHOL CONSUMPTION AND RISK OF SPECIFIC CANCERS

Sections B.3.1 to **B.3.11** review the evidence from the selected key systematic reviews for each specific cancer type in turn. When interpreting the evidence, one must be mindful of the limitations inherent in meta-analyses of epidemiological studies. Misclassification of exposure is a common methodological challenge encountered. There is a potential source of bias if light, infrequent, or ex-drinkers are classified as non-drinkers, and the risk associated with alcohol consumption is estimated relative to this group (relative risk 1.0). Additionally, there are limitations introduced through survey methodology. Most survey methods used to capture a person's alcohol consumption are based on self-report. Consequently, such surveys are subject to both intentional and unintentional errors of recall by the respondent, potentially resulting in inaccurate information. Due to the strong social stigma that alcohol drinking carries in many populations and the issue of denial in people with alcohol dependence, it is likely that many individuals underestimate and under-report their intake of alcohol, particularly in the case of heavy consumption. This could result in an underestimation of the actual carcinogenic effect of alcohol consumption. Thus, alcohol is possibly a stronger risk factor than indicated by published studies (Stewart & Kleihaus, 2003). Prospective cohort studies have the advantage of being less vulnerable to selection and recall bias than case-control studies.

B.3.1. Alcohol consumption and cancers at any site

Although several studies have examined the relationship between alcohol consumption and the risk of cancer of any type, it is important that the findings of these studies are interpreted appropriately. It is clear from a growing body of evidence that alcohol intake is associated with specific types of cancers, indicating that particular organ systems may be more susceptible to alcohol-induced injury (eg, the oesophageal mucosa) or that particular mechanisms may play a more critical role in specific tissues (eg, perturbation of oestrogen status and the development of breast cancer). Putative biological mechanisms are discussed in **Section C**. It is important to recognise that the relationship between alcohol consumption and 'all cancers' may be heavily skewed by cancers at a limited number of sites, and therefore the results may not be generalisable to all cancers.

Evidence from key systematic review

Bagnardi *et al* (2001a) conducted a comprehensive systematic review and meta-analysis of alcohol intake and the risk of various cancer types. Case-control and cohort studies were included in the meta-analysis if they provided sufficient information to estimate risk at at least three levels of alcohol consumption. According to an earlier publication from the same authors (Corrao *et al*, 1999), where reported in individual studies, one alcoholic drink was taken to be equivalent to 11.5 g alcohol. In Australia, one standard drink is considered to contain 10 g alcohol. The three alcohol categories reported in the Bagnardi review and how they compare with Australian guidelines (NHMRC, 2001) are shown in **Table 7**. As evidenced from the table, the lowest and highest consumption categories fit

with low risk and high risk drinking, respectively, in men and women according to 2001 NHMRC criteria. However, appropriate interpretation of the middle category (50 g/day) is less clear.

Table 7 Alcohol consumption categories relative to Australian guidelines

	Alcohol consumption category (Bagnardi et al)		
	25 g/day	**50 g/day**	**100 g/day**
Equivalent drinks/day according to Bagnardi *et al*	~2	~4	~8
Equivalent drinks/day according to NHMRC	2.5	5	10
Risk of harm in the long-term according to NHMRC guidelines (2001)	Men: low risk Women: low to risky	Men: risky Women: high risk	Men: high risk Women: high risk

Abbreviations: NHMRC, National Health and Medical Research Council

Bagnardi and colleagues identified eight studies (including six cohort studies and two case-control studies) that examined the risk of alcohol intake and cancer at any site. No citations or details of the individual studies were provided in the publication and therefore it is not known if any of the included studies were Australian. No significant increase in risk was observed for the lowest alcohol consumption category analysed (25 g/day, corresponding to two drinks per day). However, a significant association was seen with higher alcohol consumption. For 50 g alcohol per day the pooled RR was 1.22 (95% CI 1.11-1.27), rising to RR 1.91 (95% CI 1.77-2.06) for 100 g alcohol per day (**Table 8**). The authors state that significant effects were found from intakes of 28 g per day. Although evidence of significant heterogeneity ($P< 0.05$) was noted, the inclusion of a gender term in the meta-regression models showed no evidence of a significant gender effect. The authors made no attempt to explore other possible sources of heterogeneity such as study design or age.

Table 8 Alcohol consumption and risk of cancer (all sites): meta-analyses from Bagnardi et al (2001)

Cancer site	**# studies (cases)**	**Pooled RR (95% CI) associated with alcohol intake**		
		25 g/day	**50 g/day**	**100 g/day**
All sites together	8 (14,495)	1.01 (0.90, 1.05)	1.22 (1.11, 1.27)	1.91 (1.77, 2.06)

Abbreviations: CI, confidence interval; RR, relative risk

B.3.2. Alcohol consumption and upper aero-digestive tract cancers

There is strong longstanding epidemiological evidence that alcohol increases the risk of cancers of the upper aero-digestive tract. A causal relationship between high alcohol consumption and squamous-cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus has been noted since the mid 1950's (IARC, 1988), and a synergism between alcohol intake and tobacco smoking was reported in the 1970's. A carcinogenic effect of alcohol independently from that of smoking was first reported in 1961 (IARC, 1988). Subsequent studies have shown a reasonably consistent dose-response relationship

between alcohol consumption and risk of upper aero-digestive tract cancers for non-smokers. The strengths of these associations appear to vary from site to site, possibly due in part to the extent of physical contact between the agent and target tissue (Tuyns *et al*, 1988).

Evidence from key systematic reviews

The most comprehensive systematic review and meta-analysis of alcohol intake and the risk of various aero-digestive cancers was undertaken by Bagnardi *et al* (2001a). This review was an update of an earlier meta-analysis reported by the same authors, which evaluated the effect of alcohol on the risk of cancer at various sites (Corrao *et al*, 1999). Case-control and cohort studies were included in the meta-analysis if they considered at least three levels of alcohol consumption and reported the number of cases and non-cases or estimates of the odds ratios (OR) or relative risks (RR) for each exposure level. Although not explicitly stated, it is assumed that the reported risk estimates are relative to non-alcohol drinkers. The authors acknowledge that misclassification of former drinkers could lead to an underestimate of the real association.

As shown in **Table 9**, strong direct trends in risk were observed for all upper aero-digestive tract cancers (oral cavity and pharynx, oesophagus, larynx), and there was no safety threshold below which an effect is not evident.

Oral cavity and pharynx: Twenty-six studies (one cohort and 25 case-control, with a total of 7,954 cases) were included in the meta-analysis of cancers of the oral cavity and pharynx. A strong dose-response relationship was evident; the pooled RR associated with alcohol intake of 25 g per day (low risk drinking according to Australian guidelines) was 1.75 (95% CI 1.70-1.82), rising to 6.01 (95% CI 5.46-6.62) with high risk intake of 100 g per day (**Table 9**). Significant heterogeneity ($P< 0.05$) was noted between the studies, which could not be explained on the basis of gender.

Because aero-digestive tract cancers are known to be strongly tobacco-related, the authors investigated the potential modifying effects of smoking on the reported risk estimates by comparing pooled estimates based on risks adjusted and unadjusted for tobacco. Allowance for tobacco only marginally modified the RR (**Table 9**).

Oesophagus: Meta-analysis of alcohol intake on risk of oesophageal cancer included 28 studies (one cohort and 27 case-control) with a total of 7,239 cases. The pooled RR was 1.51 (95% CI 1.48-1.55) for alcohol intake of 25 g/day increasing to 4.23 (95% CI 3.91-4.59) for 100 g/day (**Table 9**). A significant ($P< 0.05$) gender effect in modifying the effect of alcohol intake was noted, with higher risks in women (**Table 9**). Effects of smoking adjustment in modifying the effect of alcohol related risks did not reach statistical significance.

Larynx: Twenty studies were meta-analysed to examine the association between alcohol intake and risk of laryngeal cancer. A total of 3,759 cases were included in these studies, all of which were case-control. Consistent with the analyses of other cancers of the upper aero-digestive tract, a strong dose-dependent relationship between alcohol intake and cancer incidence was observed. The pooled RR for 25 g alcohol per day was 1.38 (95% CI 1.32-1.45) rising to 3.95 (95% CI 3.43-4.57) for 100 g alcohol per day (**Table 9**). Although there was no gender effect in modifying the effect of alcohol intake, the effect of smoking adjustment reached statistical significance ($P< 0.05$), with higher risks for unadjusted estimates (**Table 9**). Evidence of a substantial alcohol-related risk persisted in the analyses of pooled studies reporting both unadjusted and adjusted estimates. Thus, although allowance for tobacco appreciably modified the relationship with laryngeal cancers, the adjusted pooled estimates confirm that for oral and pharyngeal cancers, and for oesophageal cancers, alcohol drinking has an independent effect.

Table 9 Alcohol consumption and risk of cancers of the upper aero-digestive tract: meta-analyses from Bagnardi et al (2001)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Oral cavity & pharynx	26 (7,954)	1.75 (1.70, 1.82)	2.85 (2.70, 3.04)	6.01 (5.46, 6.62)
Tobacco-unadjusted	-	1.74 (1.67, 1.81)	2.80 (2.59, 3.04)	5.82 (5.00, 6.77)
Tobacco-adjusted	-	1.76 (1.69, 1.82)	2.87 (2.68, 3.08)	6.10 (5.45, 6.83)
Oesophagus	28 (7,239)	1.51 (1.48, 1.55)	2.21 (2.11, 2.31)	4.23 (3.91, 4.59)
Males	18 (3,310)	1.43 (1.38, 1.48)	1.98 (1.87, 2.11)	3.49 (3.14, 3.89)
Females	5 (304)	1.52 (1.42, 1.63)	2.24 (1.95, 2.58)	4.45 (3.37, 5.87)
Tobacco-unadjusted	-	1.50 (1.47, 1.55)	2.19 (2.08, 2.31)	4.18 (3.79, 4.60)
Tobacco-adjusted	-	1.52 (1.46, 1.57)	2.23 (2.09, 2.38)	4.31 (3.84, 4.85)
Larynx	20 (3,759)	1.38 (1.32, 1.45)	1.94 (1.78, 2.11)	3.95 (3.43, 4.57)
Tobacco-unadjusted	-	1.65 (1.55, 1.76)	2.74 (2.43, 3.09)	7.45 (6.04, 9.18)
Tobacco-adjusted	-	1.29 (1.23, 1.36)	1.68 (1.53, 1.84)	2.79 (2.36, 3.30)

Abbreviations: CI, confidence interval; RR, relative risk

Although the Bagnardi *et al* (2001a) meta-analysis made no attempt to assess the quality of the included studies, a subsequent publication from the same authors included only those studies considered to be of high quality and showed similar direct trends in risk for upper aero-digestive tract cancers (Corrao *et al*, 2004). To reduce heterogeneity, the authors selected studies that met *a priori*-defined quality criteria and reported estimates adjusted for the main risk indicators. As for the comprehensive meta-analysis reported by Bagnardi *et al* (2001a), consistent and significant increased RRs were observed for cancers of the oral cavity and pharynx, oesophagus, and larynx, with no evidence of a threshold effect (**Table 10**).

Table 10 Alcohol consumption and risk of cancers of the upper aero-digestive tract: meta-analyses from Corrao et al (2004)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Oral cavity & pharynx	15 (4,507)	1.86 (1.76, 1.96)	3.11 (2.85, 3.39)	6.45 (5.76, 7.24)
Oesophagus	14 (3,233)	1.39 (1.36, 1.42)	1.93 (1.85, 2.00)	3.59 (3.34, 3.87)
Larynx	20 (3,789)	1.43 (1.38, 1.48)	2.02 (1.89, 2.16)	3.86 (3.42, 4.35)

Abbreviations: CI, confidence interval; RR, relative risk

The strength of the associations between alcohol and tobacco exposures and risks of aero-digestive cancers was specifically investigated in a systematic review and meta-analysis conduced by Zeka *et al* (2003). The objective was to produce summary risk estimates with uniform methods and on uniform exposure scales so that the magnitudes of the risks could be compared across tumour site (oropharynx, pharynx, larynx, and oesophagus). Studies were included if they (i) reported the drinking and smoking habits of participants, (ii) presented either the joint or independent effects of alcohol and tobacco on cancers of the upper aero-digestive tract, (iii) expressed data in terms of intensity of exposure which could be converted to grams of alcohol and of tobacco consumed per day, (iv) presented the number of subjects in each joint smoking/drinking category, and (v) used a true unexposed reference group (non-smokers and non-drinkers).

So that issues of interaction could be investigated, initial meta-regression modelling was conducted using those studies that provided effect estimates by joint categories of alcohol and tobacco. Analysis of six studies presenting such information (of 30 identified studies) found that the effects of alcohol and tobacco were substantially independent ie, on the log odds ratio scale there were no important departures from additivity of the main effects of alcohol and tobacco consumption on the upper aero-digestive tract cancer risk.

Based on these results, the data was expanded to include all studies which had investigated the independent effects of alcohol and/or tobacco, while controlling for the other. Studies were selected if (i) alcohol analyses controlled adequately for tobacco consumption and tobacco analyses controlled adequately for alcohol consumption, (ii) there was control for potential confounding by age, gender, and when appropriate race, (iii) confidence intervals were provided for the estimated effects, and (iv) there were at least three strata for each exposure. Fourteen studies met the final selection criteria. The exposure-risk slopes for each study were combined, site by site, using random effects meta-regression methods. Pooled estimates of the effect of alcohol at each site were informed by between one and eight studies: two studies for cancer of the oropharynx, one study for pharynx, four studies for larynx, and eight studies for oesophagus. Tobacco estimates were informed by two studies each for cancers of the oropharynx and pharynx, four studies for cancer of the larynx, and eight studies for cancer of the oesophagus. Whilst studies of the oropharynx and pharynx showed no heterogeneity for either alcohol

or tobacco, there was significant heterogeneity between studies for the effects of alcohol ($P< 0.01$) and tobacco ($P< 0.05$) on the larynx and oesophagus.

The effect of alcohol on the oesophagus appeared to depend strongly on cell type, with a greater risk of squamous cell carcinoma than adenocarcinoma. In contrast, the effects of tobacco were quite similar on the two cell types. Consistent with the Bagnardi *et al* review (2001a), alcohol's effect was strongest on the pharynx than on any of the other aero-digestive sites. Tobacco appeared to have a much stronger effect on the larynx. The weakest association was that of alcohol and adenocarcinoma of the oesophagus, which was an order of magnitude weaker than that for tobacco and laryngeal cancer.

Risks rose very steeply with increasing quantities of alcohol and tobacco. Laryngeal and pharyngeal cancer risks were increased about 35-fold for the highest joint category of alcohol and tobacco consumption (**Table 11**). The least affected among the upper aero-digestive tract cancers - oesophageal cancer - had about a 13-fold increase in risk from the highest combined category of consumption compared to the non-exposed. The publication did not provide confidence intervals for the risk estimates.

Table 11 Alcohol and tobacco consumption and risk of cancers of the upper aero-digestive tract: meta-analyses from Zeka et al (2003)

Tobacco consumption	Cancer site	OR associated with alcohol intake		
		0 drinks/day	>0-4 drinks/day	4+ drinks/day [a]
0 cigarettes/day	Oropharynx	1.0	1.5	7.2
	Pharynx	1.0	1.7	12.6
	Larynx	1.0	1.4	4.5
	Oesophagus [b]	1.0	1.4	4.2
>0-30 cigarettes/day	Oropharynx	1.3	2.0	9.7
	Pharynx	1.3	2.3	16.7
	Larynx	1.8	2.4	7.9
	Oesophagus [b]	1.4	1.8	5.6
30+ cigarettes/day [a]	Oropharynx	2.9	4.5	21.2
	Pharynx	2.8	4.8	35.6
	Larynx	7.7	10.6	34.6
	Oesophagus [b]	3.1	4.1	12.7

Abbreviations: CI, confidence interval; RR, relative risk
[a] Midpoints for the upper categories: 55 for cigarettes per day and 9.5 drinks per day
[b] Squamous cell carcinoma and mixed cell type

In a recent study, researchers at IARC sought to tease out the independent effect of alcohol and cigarette smoking on head and neck cancer development (Hashibe *et al*, 2007). The authors conducted a pooled analysis of data from 15 case-control studies of head and neck cancer risk and cigarette smoking among never drinkers, and head and neck cancer risk and alcohol drinking among never users of tobacco. The analysis included 10,244 head and neck cancer patients and 15,227 controls.

Approximately 16% of patients and 27% of controls never drank, and about 11% of patients and 38% of controls never smoked.

Cigarette smoking was associated with an increased risk of head and neck cancer, especially cancer of the larynx, among patients who never drank alcohol (Hashibe *et al*, 2007). There were clear dose-response relationships for the frequency, duration, and number of pack-years of cigarette smoking. Among never users of tobacco, high-frequency alcohol consumption (ie, three or more drinks per day) was associated with increased risks of cancers of the oropharynx/hypopharynx and larynx only. Whereas approximately 24% of head and neck cancers were attributable to smoking among patients who never consumed alcohol, approximately 7% of head and neck cancers were attributable to drinking among never smokers.

Evidence from studies published since the key systematic review

A considerable number of primary studies investigating the association between alcohol consumption and risk of cancer of the upper aero-digestive tract have been published since the key systematic review by Bagnardi *et al* (**Table 12**). Based on a review of the abstracts from these studies (all of which were case-control), the newer evidence is generally consistent with the systematic reviews. There is consistent evidence for a synergistic effect of alcohol and smoking on the risk of cancers of the upper aero-digestive tract. However, there is some evidence to suggest that the association between alcohol consumption and risk of oesophageal cancer may be restricted to squamous cell carcinoma but not adenocarcinoma (Lagergren *et al*, 2000; Hashibe *et al*, 2007). There was no consistent message regarding a differential effect by beverage type.

Two of the publications listed in **Table 12** are scientific papers from IARC (both reported by Hashibe *et al*, 2007). Both publications are from a multicentre case-control study conducted in Central and Eastern Europe to investigate the role of tobacco and alcohol as causes of head and neck cancer in the region. Whilst the authors reported that alcohol use alone was not significantly associated with an increased risk of developing laryngeal cancer or adenocarcinoma of the oesophagus, the risk of squamous cell carcinoma of the oesophagus was found to be increased three-fold in ever drinkers, and nearly 40% of laryngeal cancers were attributed to the interaction between alcohol and tobacco.

The study reported by Dal Maso and colleagues (2002) investigated drinking pattern with respect to food consumption and risk of cancers of the upper aero-digestive tract in a series of case-control studies conducted in Italy and Switzerland. After adjustment for potential covariates and allowance for differences in alcohol intake levels, the authors reported that drinking alcohol with meals did not eliminate cancer risk at any of the sites. However, individuals who also drank alcoholic beverages outside meals showed an increased risk of developing cancers of the upper aero-digestive tract compared with those who drank with meals only. Individuals who drank a significant portion of their

alcohol outside meals had at least a 50-80% higher risk of cancer of the oral cavity, pharynx, and oesophagus, and a 20% higher risk of laryngeal cancer when compared with people who drank only at meals. The authors postulated that food reduces cancer risks either by partially coating digestive-tract tissues or by washing alcohol off those tissues. Furthermore, they speculated that the reason laryngeal risks were dramatically lower for all study participants is due to the tissue's lower exposure to alcohol. Rather than swallowed liquid washing across the larynx, contact with alcohol is made through vapours that escape from the ingested liquid.

Table 12 Brief summary of newer studies of alcohol consumption and risk of cancers of the upper aero-digestive tract, by year of publication

Cancer type	Author	Study type	Country	Participants	Findings in relation to cancer risk
oesophageal	Bosetti *et al*, 2000	2 case-control studies	Italy	714 cases & 3137 hospital controls	Increased risk with alcohol intake; association for wine but not beer or spirits
oral & pharyngeal	Bosetti *et al*, 2000	2 case-control studies	Italy & Switzerland	195 cases & 1113 controls	Increased risk with high intake
oral & pharyngeal	Franceschi *et al*, 2000	case-control	Italy & Switzerland	754 cases & 1775 controls	Increased risk with alcohol intake, not affected by duration of drinking
oesophageal	Lagergren *et al*, 2000	case-control	Sweden	618 cases & 820 hospital controls	Increased risk of SSC with alcohol intake, synergistic with smoking. No association with oesophageal or cardia adenocarcinoma.
oral	Moreno-Lopez *et al*, 2000	case-control	Spain	75 cases & 150 population controls	Increased risk with alcohol intake
oral, pharyngeal, laryngeal	Schlecht *et al*, 2001	case-control	Brazil	784 cases & 1578 hospital controls	Increased risk with alcohol intake, particularly liquor
oral	Schwartz *et al*, 2001	case-control	US	333 cases & 541 population controls	Increased risk with alcohol intake, higher in ADH3*2 homozygotes
laryngeal	Altieri *et al*, 2002	case-control	Italy & Switzerland	527 cases & 1297 hospital controls	Risk decreased only ≥20 yrs after drinking cessation
oral, pharyngeal, oesophageal, laryngeal	Dal Maso *et al*, 2002	series of case-control studies	Italy & Switzerland	1498 cases & 3263 controls	Increased risk with drinking outside meals
laryngeal	Talamini *et al*, 2002	case-control	Italy and Switzerland	527 cases & 1297 hospital controls	Increased risk with alcohol intake, synergistic with smoking
oral & pharyngeal	Huang *et al*, 2003	case-control	Puerto Rico	286 cases & 417 population controls (men only)	Increased risk with heavy liquor intake, modest effects with beer & wine.
oesophageal	Yokoyama *et al*, 2003	case-control	Japan	233 cases & 610 controls (men only)	Increased risk with alcohol intake, higher in those who reported current 'alcohol flushing'
oral & pharyngeal	Altieri *et al*, 2004	case-control	Italy & Switzerland	749 cases & 1772 hospital controls	Increased risk with alcohol intake, higher risk in wine drinkers than spirits/beer
laryngeal	Garavello *et al*, 2006	case-control	Italy	672 cases & 3454 hospital controls	Increased risk in drinkers, particularly wine
oesophageal	Wu *et al*, 2006	case-control	Taiwan	165 cases & 255 hospital controls	Increased risk with alcohol consumption

Cancer type	Author	Study type	Country	Participants	Findings in relation to cancer risk
oral & pharyngeal	De Stefani *et al*, 2007	case-control	Uruguay	776 cases & 1501 controls	Increased risk, varying with cancer site
oesophageal	Hashibe *et al*, 2007	case-control	Central & Eastern Europe	227 cases & 1114 hospital controls	Increased risk of SSC (but not adenocarcinoma) with alcohol intake, synergistic with smoking.
laryngeal	Hashibe *et al*, 2007	case-control	Central & Eastern Europe	384 cases & 918 hospital controls	Synergistic effect between alcohol and smoking
oesophageal	Lee *et al*, 2007	case-control	Taiwan	652 cases & 1127 hospital controls	Increased risk with heavy consumption in non-smokers, synergistic with smoking
oesophageal	Wang *et al*, 2007	case-control	China	355 cases & 408 population controls	Increased risk with alcohol intake in men but not women

Abbreviations: SCC, squamous cell carcinoma
NOTE: The key systematic review and meta-analysis (Bagnardi *et al*, 2001a) reported a literature search date range of 1966 to 2000, with no details of the included studies. Therefore, there may be some overlap between the included studies in Bagnardi *et al* and those published in the year 2000 in the table above.

B.3.3. Alcohol consumption and breast cancer

Intense epidemiological research has been directed at understanding the relationship between breast cancer and the consumption of alcohol. The bulk of the evidence indicates a positive association between alcohol and risk of breast cancer, although the magnitude of the risk is variable. In NSW, breast cancer is responsible for approximately 27% of all cancers in women (Tracey *et al*, 2006). Given its high incidence (114.0 per 100,000 women in NSW, age-standardised), even a small excess risk of breast cancer due to alcohol, if causal, has serious public health implications considering that alcohol consumption is one of the few modifiable risk factors associated with breast cancer. However, this depends upon the level of alcohol intake at which the risk of breast cancer is significantly increased and the profile of alcohol intake amongst Australian women. According to a report from the Australian Government Department of Health and Ageing, *Australian women and alcohol consumption 1996-2003* (Young & Powers, 2005), the clear majority of Australian women are low-risk drinkers (**Table 13**), defined using NHMRC 2001 criteria (see **Table 2**). This is supported by data from the *2006 New South Wales Population Health Survey* (Centre for Epidemiology and Research, 2007) which showed that only 12.6% of women aged 16 years and over reported risky or high risk drinking behaviour. However, as mentioned in **Section A.3.1**, 'low risk' drinking according to the NHMRC Guidelines takes into consideration all health risks and benefits associated with alcohol consumption. Risk of breast cancer may be increased at drinking levels considered to be 'low risk'.

Table 13 Alcohol consumption in Australian women related to long-term risk drinking

Age cohort	Consumption category			
	Non-drinkers	Rarely drank	Low risk drinkers	Risky or high risk drinkers
Younger women aged 18-23 years (n=14,247)	9%	34%	52%	5%
Mid-age women aged 45-50 years (n=13,716)	15%	31%	50%	5%
Older women aged 70-75 years (n=12,432)	34%	29%	34%	3%

Source: Australian Longitudinal Study on Women's Health (ALSWH) (Young & Powers, 2005)

Evidence from key systematic reviews

Key *et al* (2006) conducted a comprehensive systematic review and meta-analysis to provide robust, quantitative estimates of the alcohol-breast cancer association as a basis for guiding public health policy in the area. The authors went to considerable efforts to identify and deal with sources of bias in the published data, carrying out sensitivity analyses based on pre-defined quality criteria and controlling for confounding. A total of 98 unique studies were identified in the literature search, including 75 retrospective case-control studies, five prospective case-control studies, and 18 prospective cohort studies. Two of the retrospective case-control studies (both of which used community controls) were Australian. The meta-analysis of drinkers versus non-drinkers included 89 studies based on 75,728 cases. Seventy-one studies (60,653 cases) were included in the analysis of dose-response. Based on the epidemiological evidence, the authors showed a positive association between alcohol consumption and risk of breast cancer which could not be readily explained by bias or confounding. Although results varied across the sensitivity analyses performed, positive and significant associations were found in all analyses, indicating that the findings are consistent over a range of scenarios.

All previous meta-analyses (see **Table 3**) reported a positive association between alcohol consumption and breast cancer. However, the review by Key and colleagues was considered superior because it included (i) non-English publications, (ii) an assessment of the association of drinking alcohol versus not drinking alcohol, (iii) sensitivity analysis on quality of included studies and adjustments for cofounders, (iv) exploration of the risk by type of alcoholic beverage, (v) assessment of the dose-response relationship among drinkers (ie, excluding non-drinkers), (vi) comparison of the results with those of the large Oxford meta-analysis of individual patient data (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). In addition, the authors included an estimation of population attributable risk (among drinkers of alcohol in the USA and UK). The literature search conducted by Key and colleagues used a variety of methods to minimise publication bias, including citation searching, identification of the grey literature, and searches of conference proceedings. The authors used a simple scoring system to identify studies with potential biases due to design issues or

confounding so that they could be excluded in sensitivity analyses. The quality criteria were not used as part of the regression analyses or as weights, because of the potential for this to introduce bias.

The results of the meta-analysis of all 89 studies with sufficient data showed that compared with non-drinkers, the estimated risk of breast cancer is 11% higher in women who drink alcohol (OR 1.11, 95% CI 1.06-1.17). This increased risk rose to 22% in a sensitivity analysis of the 19 studies with the highest study quality score (determined by the authors), with multivariate adjustment for confounders (**Table 14**). It is noteworthy that the authors assigned the highest quality score to studies with acceptable design and adequate control for confounding, defined as control for three or more of the following variables: a reproductive characteristic (such as age at menarche, age at menopause, age at first birth, parity), family history of breast cancer, socio-economic status, oral contraceptive use/hormone replacement therapy.

Table 14 Alcohol consumption and risk of breast cancer: meta-analyses from Key et al (2006)

Model	Drinkers vs non-drinkers		Dose-response, per 10 g ethanol per day	
	OR (95% CI)	# studies	Percent excess risk (95% CI)	# studies
Least adjusted ORs from all studies	1.11 (1.06, 1.17)	89	12 (9, 15)	71
Beer	1.16 (1.04, 1.29)	30	nr	-
Wine	1.14 (1.05, 1.24)	32	nr	-
Spirits	1.14 (1.06, 1.23)	31	nr	-
Least adjusted ORs, studies with score 2 or 3	1.12 (1.06, 1.18)	61	13 (9, 17)	54
At least age adjusted ORs from all studies	1.17 (1.09, 1.26)	35	11 (7, 15)	41
At least age adjusted ORs, studies with score 2 or 3	1.17 (1.09, 1.26)	28	12 (8, 17)	34
Multivariate adjusted ORs from all studies	1.16 (1.10, 1.24)	54	11 (7, 14)	63
Multivariate adjusted ORs, studies with score 2 or 3	1.17 (1.10, 1.24)	42	12 (8, 16)	51
Multivariate adjusted ORs, studies with score 3	1.22 (1.09, 1.37)	19	10 (5, 15)	33

Abbreviations: CI, confidence interval; nr, not reported; OR, odds ratio
Study quality scoring system: score 1 – studies with inadequate design (information on alcohol consumption missing for at least 30% of participants, results not adjusted for age, for case-control studies response rate < 60%, for cohort studies loss to follow-up > 30%); score 2 – studies with acceptable design but insufficient control for confounding; score 3 – studies with acceptable design and adequate control for confounding, defined as control for three or more of the following variables: a reproductive characteristic (such as age at menarche, age at menopause, age at first birth, parity), family history of breast cancer, socio-economic status, oral contraceptive use/hormone replacement therapy.

Where relevant data were available, the authors analysed data separately for drinkers versus non-drinkers of beer (30 studies), wine (32 studies), and spirits (31 studies). Combined least adjusted odds ratios were estimated to be 1.16 (95% CI 1.04-1.29) for beer, 1.14 (95% CI 1.05-1.24) for wine, and 1.14 (95% CI 1.06-1.23) for spirits (**Table 14**), indicating that the risk does not differ with beverage type.

Meta-analysis of dose-response in the 71 studies with sufficient data showed that amongst drinkers, the excess risk associated with drinking an extra 10 g of ethanol a day (ie, one standard drink) is 12% (95% CI 9-15%)(**Table 14**). In a sensitivity analysis including the 33 studies with the highest study quality

score, with multivariate adjustment for confounders, the excess risk was estimated to be slightly lower at 10% (95% CI 5-15%). Despite significant methodological differences, these results are comparable to the Oxford collaborative re-analysis of individual patient data from 53 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 2002), which showed a 7.1% (95% CI 5.5-8.7%) higher risk for each additional 10 g ethanol per day.

An important feature of the dose-response analysis was the use of a variable intercept model. Non-drinkers were excluded and therefore the dose-response curve was not constrained to go through origin. This is an important consideration when the reference group (non-drinkers) is contaminated to some extent by the inclusion of ex-drinkers, occasional drinkers, or light drinkers, as was the case in many of the studies analysed.

All analyses showed significant heterogeneity ($P< 0.05$) across studies in size of the association between alcohol consumption and risk of breast cancer. To explore possible sources of heterogeneity, the authors entered various factors into meta-regression analyses. In the analysis of drinkers versus non-drinkers, retrospective case-control studies with hospital controls were associated with significantly ($P< 0.05$) higher odds ratio estimates than those with community controls. However, this significant difference between hospital and community controls was not seen in the dose-response analyses. None of the other variables examined in meta-regression (ie, whether the data were collected before or after disease onset, pre-/post-menopausal status, or nationality of the study population) significantly reduced the heterogeneity across studies. Likewise, the Oxford reanalysis of individual patient data examined possible sources of confounding (race, education, family history of breast cancer, age at menarche, height, weight, body mass index, breastfeeding, use of hormonal preparations) and found that none materially altered the estimates of relative risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

The authors further tested the sensitivity of the results of the dose-response calculation by (i) fixing the first and last points of the dose-response in each study (via comparison of zero and variable intercept models and by assigning different values to the highest consumption band where these were open-ended), and (ii) using binomial logistic rather than log linear regression to estimate the dose-response curve at the study level. Sensitivity to alternative choice of controls was also tested, where these were reported. None of these sensitivity analyses appreciably altered the results. Furthermore, there was no indication that smaller studies (with larger confidence intervals) were more positive. Funnel plots did not indicate any evidence for publication bias, including for subset analyses.

Unlike other published meta-analyses, the study by Key *et al* did not attempt to analyse data according to alcohol consumption categories. In a comprehensive series of meta-analyses reported by Bagnardi *et al* (2001a,b), the relationship between alcohol intake and the risk of cancer was investigated at various

anatomical sites. Bagnardi and colleagues estimated the risk of different cancer types for each of three exposure levels: 25 g ethanol per day (corresponding to approximately two drinks per day), 50 g ethanol per day (four drinks per day), and 100 g ethanol per day (eight drinks per day). For the analysis of breast cancer, 49 studies (totalling 44,033 cases), including 12 cohort and 37 case-control studies were included. Based on multivariate estimates directly obtained from a meta-regression model of best fit, the authors found a statistically significant association between alcohol consumption and breast cancer for all three exposure levels, including the lowest ie, 25 g alcohol per day (**Table 15**).

A similar association was noted in a publication from the same authors (Corrao *et al*, 2004), which selectively included only those studies that met pre-defined quality criteria based on study design, data collection methods for alcohol consumption, and data analysis. A total of 29 studies (24 case-control and 5 cohort) including 32,175 cases were included in the analysis (**Table 15**).

Table 15 Alcohol consumption and risk of breast cancer: meta-analysis from Bagnardi and colleagues

Author (year)	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Bagnardi (2001a,b)	49 (44,033)	1.31 (1.27, 1.36)	1.67 (1.56, 1.78)	2.71 (2.33, 3.08)
Corrao (2004)	29 (32,175)	1.25 (1.20, 1.29)	1.55 (1.44, 1.67)	2.41 (2.07, 2.80)

Abbreviations: CI, confidence interval; RR, relative risk

The relationship between alcohol intake and breast cancer was examined in an Australian context by Ridolfo & Stevenson (2001), who updated an earlier Australian meta-analysis reported by English *et al* (1995). Consistent with the meta-analyses described above, the revised RR estimates showed a statistically significant relationship between alcohol consumption and risk of breast cancer, evidenced at low levels of alcohol intake (**Table 16**). Analysis by age showed no statistical difference in risks for women of pre-menopausal age (ie, under the age of 45 years) or post-menopausal age (ie, 45 years or older). The revised overall adult female aetiological fraction for breast cancer caused by low, medium, and high drinking levels was estimated to be 0.121, based on prevalence estimates from the Australian Bureau of Statistics (ABS) National Health Survey. Thus, approximately 12% of female breast cancer for ages 18 years and over may be attributable to low, medium, and high levels of alcohol intake.

Table 16 Alcohol consumption and risk of breast cancer: meta-analysis from Ridolfo & Stevenson (2001)

Analysis	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		Low	Medium	High
All studies	45 (nr)	1.14 (1.09, 1.20)	1.41 (1.32, 1.50)	1.59 (1.43, 1.78)
Age < 45 years	nr	1.15 (1.04, 1.28)	1.41 (1.2, 1.67)	1.46 (0.99, 2.14)
Age ≥ 45 years	nr	1.14 (1.05, 1.24)	1.38 (1.24, 1.53)	1.62 (1.24, 2.13)

Abbreviations: CI, confidence interval; nr, not reported; RR, relative risk
NOTE: Low intake = 0.26-2 standard drinks/day (2.6-20.0 g/day), medium intake = 2-4 standard drinks/day (21.0-40.0 g/day), high intake = >4 standard drinks/day (41+ g/day).

A mounting body of epidemiologic and experimental studies has indicated that low folate intake or status is associated with elevated risk of several cancers, including breast cancer. The interaction between folate and alcohol was not addressed in the meta-analyses discussed above. However, a recent systematic review and meta-analysis of prospective and case-control studies was conducted by Larrson *et al* (2007) to examine folate intake and levels in relation to risk of breast cancer. The authors identified five prospective studies which investigated whether the association between alcohol consumption and risk of breast cancer was modified by folate intake. Whilst one study observed no interaction between folate and alcohol, the remaining four studies (with a total of 3,202 breast cancer cases among 74,808 participants) found that the increased risk of breast cancer associated with alcohol consumption was greatest in or limited to women with low folate intake. Although strong statistical evidence of an interaction is lacking, these results indicate that modest intakes of folate may attenuate the risks associated with the consumption of alcohol.

Larrson and colleagues also identified two prospective studies and two case-control studies that presented results on folate intake in relation to breast cancer risk that were stratified by alcohol consumption (Larsson *et al*, 2007). In all four studies there was a statistically significant reduction in breast cancer risk for high versus low folate intake among women who consumed moderate or high amounts of alcohol (summary estimate 0.51, 95% CI 0.41-0.63) but not among women with low (< 15 g per day) or no alcohol consumption (summary estimate 0.95, 95% CI 0.78-1.15). In two other prospective studies that did not provide risk estimates by strata of alcohol consumption, it was reported that folate intake and breast cancer risk did not vary by stratum of alcohol consumption. Thus, alcohol may be a potential modifying factor on the association between folate and breast cancer. A plausible hypothesis exists in which alcohol intake and inadequate dietary intake act synergistically to deplete serum folate levels and thus increase breast cancer risk (Halsted *et al*, 2002). However, it is noteworthy that a randomised crossover trial in which postmenopausal women received three 8-week treatments of alcohol at 0, 15, and 30 g/day in random order found that moderate alcohol intake had no effect on serum folate concentrations (Laufer *et al*, 2004). Large prospective studies that investigate interactions between folate and alcohol consumption are needed to further clarify their role in breast cancer aetiology.

Finally, none of the publications mentioned above addressed the issue of the impact of lifetime versus specific time period of risk (eg, heavier drinking among women during their 20's and 30's). This is inherently difficult to determine in observational research because of the within-person correlation in drinking patterns across time. Furthermore, assessment of the existing literature is hampered by the fact that many studies of alcohol and breast cancer did not collect data from multiple periods of use. In a recent study by Terry *et al* (2006a), which is one of the larger studies on this issue, the findings did

not support a specific time period of susceptibility relative to other time periods. The authors suggest that it is plausible that because alcohol intake can have both initiating effects via acetaldehyde as well as tumour-promoting effects, multiple time periods should be important to breast cancer risk (Terry *et al*, 2006b).

Evidence from studies published since the key systematic reviews

A considerable number of primary studies investigating the association between alcohol consumption and risk of breast cancer have been published since the literature search conducted by Key *et al* (2006), which included articles published between January 1966 and December 2003. Seven of these publications are large cohort studies with at least 50,000 participants. Based on a review of the abstracts from these studies (**Table 17**), the newer evidence is consistent with the findings of the Key *et al* meta-analysis, providing further support for a positive association between alcohol consumption and risk of breast cancer.

The largest of the newer studies is a report from The European Prospective Investigation into Cancer and Nutrition (EPIC; Tjonneland *et al*, 2007). Data from 274,688 women with 4,285 incident cases of invasive breast cancer were included in the analysis. Data were adjusted for known risk factors and stratified according to study centre as well as for potentially modifying host factors. Incidence rate ratios (IRR) were calculated using reported intake of alcohol, recent (at baseline) and lifetime exposure. A modest increase in IRR was seen per 10 g higher recent alcohol intake (IRR 1.03, 95% CI 1.01-1.05). When adjusted, no association was seen between lifetime alcohol intake and risk of breast cancer. No difference in risk was shown between users and non-users of hormone replacement therapy (HRT), and there was no significant interaction between alcohol intake and body mass index, HRT or dietary folate.

Several of the other large cohort studies identified in the updated literature search showed a higher risk in postmenopausal women (Dumeaux *et al*, 2004; Horn-Ross *et al*, 2004; Petri *et al*, 2004). Several studies also found a stronger association in women with oestrogen receptor-positive tumours (McDonald *et al*, 2004; Suzuki *et al*, 2005; Zhang *et al*, 2007). Further research is required to confirm these findings.

There was no consistent message regarding a differential effect by beverage type. However, a number of studies investigated different patterns of alcohol consumption (eg, recent intake, cumulative lifetime intake, early drinking start, or drinking before first birth) and found that an increased risk of breast cancer is associated more with recent alcohol intake (Horn-Ross *et al*, 2004; McDonald *et al*, 2004; Tjonneland *et al*, 2004). Further investigation of alcohol consumption patterns and risk of breast cancer is warranted.

It is noteworthy that one study examined the association between alcohol consumption and male breast cancer and found that risk increase by 16% per additional 10 g alcohol per day (Guenel *et al*, 2004). This is higher than the 10-13% increased risk per additional 10 g alcohol per day found for women (Key *et al*, 2006).

Table 17 Brief summary of newer studies of alcohol consumption and risk of breast cancer, by year of publication

Author	Study type	Country	Participants	Findings in relation to cancer risk
Dumeaux *et al*, 2004	cohort	Norway	86,948 women, with 1,130 cases	Increased risk, higher in postmenopausal women
Horn-Ross *et al*, 2004	cohort	US	103,460 women with 1,742 cases	Increased risk, highest in postmenopausal women with history of benign breast disease or use of HRT. Most evident with recent drinking. No association with drinking earlier in life.
Mattison *et al*, 2004	cohort	Sweden	89,602 person-years with 342 cases	Increased risk with high wine intake, but not high total alcohol intake
McDonald *et al*, 2004	case-control	US	4,575 cases & 4,682 population controls	Increased risk with recent consumption of alcohol; associated with ER+/PR- tumours
Petri *et al*, 2004	cohort	Denmark	13,074 women with 473 cases	Increased risk with alcohol intake. Increased risk with spirits in postmenopausal women.
Sellers *et al*, 2004	cohort	US	33,552 postmenopausal women with 1,823 cases	Increased risk among drinkers with low folate but not with high folate; increased risk in women with a family history, regardless of folate intake
Tjonneland *et al*, 2004	cohort	Denmark	29,875 postmenopausal women with 423 cases	Increased risk with recent alcohol intake; no association with cumulative lifetime intake, early drinking start, or start before first birth
Guenel *et al*, 2004	case-control	Denmark, France, Germany, Italy, Sweden	74 cases (in men) & 1432 population controls (men)	Increased risk with increased intake (16%, 95% CI 7-26%) per 10 g alcohol/day. For > 90 g/day, OR 5.89 (95% CI 2.21-15.69).
Lin *et al*, 2005	cohort	Japan	271,412 person-years with 151 cases	Increased risk with alcohol intake, not associated with age that drinking started
Suzuki *et al*, 2005	cohort	Sweden	51,847 postmenopausal women with 1,188 cases	Increased risk of ER+ (but not ER-) tumours with alcohol intake
Lajous *et al*, 2006	cohort	France	62,739 post-menopausal women with 1,812 cases	Decreased risk with high folate intake, not modified by alcohol intake
Tjonneland *et al*, 2007	cohort	Europe	274, 688 women with 4,285 cases	Increased risk with recent alcohol intake, unchanged with HRT use; no association with lifetime intake
Zhang *et al*, 2007	cohort	US	38,454 women with 1,484 cases	Increased risk of invasive breast cancer with alcohol intake; increased risk with ER+/PR+ tumours but not ER- or PR-

Abbreviations: ER+, oestrogen receptor-positive; HRT, hormone replacement therapy; PR+, progesterone receptor-positive

B.3.4. Alcohol consumption and colorectal cancer

Colorectal cancer is the second most common cancer in NSW, accounting for 13% of all cancers (Tracey *et al*, 2006). Thus, even a moderate excess risk may have important public health implications. A moderate association between increased alcohol intake and risk of colorectal cancer has been shown in the literature, albeit inconsistently.

Evidence from key systematic review

Recently, Moskal *et al* (2006) undertook a meta-analysis of prospective cohort studies that evaluated the relationship between total alcohol consumption and colon, rectum, or colorectal cancer incidence. The systematic literature search identified sixteen cohort studies. To be included in the dose-response meta-analysis, studies had to report associations for at least three categories of exposure and the number of cases and comparison subjects for each category. Although the authors made no attempt to evaluate the quality of the included studies, they included only prospective cohort studies which have the advantage of being less vulnerable to selection and recall bias than case-control studies.

Overall, alcohol intake was found to be positively but not significantly associated with colorectal cancer (**Table 18**). The pooled RR for the highest versus the lowest alcohol category was 1.34 (95% CI 0.92-1.96). The lowest category was often 'non-drinker' but in one study ranged from 0.01-5.3 g/day. The highest consumption category ranged across studies from >7 drinks/week (ie, >1 drink/day) to ≥300 g/week in men (ie, >4 drinks/day). The results were heterogeneous across cohorts, with two studies reporting a significantly increased risk in men and the remaining studies reporting no significant association. Meta-analysis by gender showed that high alcohol intake was significantly associated with colorectal cancer in men (RR 1.73, 95% CI 1.00-2.98) but not women (RR 0.88, 95% CI 0.61, 1.27) (**Table 18**).

When analysed by cancer site, alcohol was significantly associated with colon cancer, with a RR of 1.50 (95% CI 1.25-1.79) for the highest versus the lowest alcohol category (**Table 18**). The results were heterogeneous, with 10 cohort studies reporting a significant positive association, five studies reporting positive non-significant relationships, and two studies reporting non-significant inverse relationships between alcohol intake and colon cancer incidence. As for colorectal cancer, meta-analysis by gender showed that alcohol consumption was positively associated with colon cancer in men but not women (**Table 18**). In meta-regression analysis, geographical area was a significant source of heterogeneity between studies.

Alcohol intake was significantly positively associated with rectal cancer, with a RR of 1.63 (95% CI 1.35-1.97) for the highest versus the lowest alcohol category (**Table 18**). There was no heterogeneity

across the 14 included datasets. The association with cancer of the rectum was significant in men (RR 1.79, 95% CI 1.38-2.33) but not in women (RR 1.39, 95% CI 0.95-2.02) (**Table 18**).

Table 18 Alcohol consumption and risk of cancers of the colon and rectum: meta-analysis from Moskal et al (2006)

Subgroup	Colorectal		Colon		Rectum	
	# studies [a]	RR (95% CI)	# studies [a]	RR (95% CI)	# studies [a]	RR (95% CI)
For highest versus lowest level of alcohol intake						
All studies	7	1.34 (0.92, 1.96)	17	1.50 (1.25, 1.79)	14	1.63 (1.35, 1.97)
Men	3	1.73 (1.00, 2.98)	8	1.64 (1.39, 1.93)	7	1.79 (1.38, 2.33)
Women	3	0.88 (0.61, 1.27)	5	1.23 (1.00, 1.51)	4	1.39 (0.95, 2.02)
Both sexes	1	1.53 (0.87, 2.69)	4	1.33 (0.97, 1.83)	3	1.54 (1.00, 2.37)
For an increase of 100 g of alcohol intake per week						
All studies	7	1.19 (1.14, 1.27)	14	1.15 (1.07, 1.23)	12	1.15 (1.10, 1.21)
Men	3	1.21 (1.02, 1.43)	7	1.18 (1.13, 1.24)	6	1.19 (1.12, 1.26)
Women	3	1.05 (0.92, 1.20)	3	1.14 (1.00, 1.30)	3	1.16 (0.94, 1.44)
Both sexes	1	1.24 (0.76, 2.01)	4	0.99 (0.94, 1.05)	3	1.10 (1.02, 1.19)

Abbreviations: CI, confidence interval; RR, relative risk

[a] Studies that provided separated analyses for men and women were analysed as two separate cohorts.

Fourteen cohort studies were included in the dose-response analysis. There was a 19% increased risk of colorectal cancer associated with an increase of 100 g of alcohol per week (equivalent to 1-2 standard drinks per day), with a RR of 1.19, 95% CI 1.14-1.27 (**Table 18**). The RR for colon cancer was 1.15 (95% CI 1.07-0.23) for a 100 g/week increase in alcohol intake. The dose-response relationship was statistically significant in men and women. Meta-regression identified geographical area as a possible source of heterogeneity. For rectal cancer, there was a 15% increased risk associated with an increase of 100 g of alcohol per week (RR 1.15, 95% CI 1.10-1.21), and a statistically significant relationship in men but not in women (**Table 18**). No inconsistencies were observed across geographical areas.

The dose-response relationship for rectal cancer was of similar magnitude to that observed for colon cancer. Although statistically significant, the increased risk of cancers of the colon and rectum associated with 25 g alcohol intake per week was small in magnitude, increasing to a 15% increased risk with alcohol intake of 100 g per week (equivalent to approximately 14 g per day) (**Table 19**). Considering the low levels of intake analysed in this review (ie, 25-100 g per week rather than per day), these results are higher than other estimates from the literature.

A meta-analysis reported by Bagnardi *et al* (2001a) showed a direct relationship between alcohol intake and cancers of the colon and rectum (**Table 19**). In addition to cohort studies, the meta-analysis conducted by Bagnardi *et al* included case-control studies that considered at least three levels of alcohol consumption. Twenty-two studies (six cohort and 16 case-control studies with a total of 11,296 cases) were included in the meta-analysis. The pooled RR for cancers of the colon and rectum was 1.08 (95%

CI 1.06-1.10) for 25 g alcohol per day rising to 1.38 (95% CI 1.29-1.49) for 100 g alcohol per day (**Table 19**). The publication states that allowance for tobacco had a negligible effect on the estimates for colorectal cancer. The same authors subsequently reported the results separately for cancer of the colon and rectum (Corrao *et al*, 2004), showing slightly higher risk estimates for rectal compared with colon cancer, more evident with heavy consumption (**Table 19**).

Table 19 Alcohol consumption and risk of cancers of the colon and rectum: dose-response relationship from Moskal et al (2006), Bagnardi et al (2001), and Corrao et al (2004)

Author (year)	Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
Alcohol consumption categories			**25 g/week**	**50 g/week**	**100 g/week**
Moskal *et al* (2006)	Colon	14 (nr)	1.03 (1.02, 1.05)	1.07 (1.03, 1.11)	1.15 (1.07, 1.23)
	Rectum	12 (nr)	1.04 (1.02, 1.05)	1.07 (1.05, 1.10)	1.15 (1.10, 1.21)
Alcohol consumption categories			**25 g/day**	**50 g/day**	**100 g/day**
Bagnardi *et al* (2001a)	Colon & rectum	22 (11,296)	1.08 (1.06, 1.10)	1.18 (1.14, 1.22)	1.38 (1.29, 1.49)
Corrao *et al* (2004)	Colon	16 (5,360)	1.05 (1.01, 1.09)	1.10 (1.03, 1.18)	1.21 (1.05, 1.39)
	Rectum	6 (1,420)	1.09 (1.08, 1.12)	1.19 (1.14, 1.24)	1.42 (1.30, 1.55)

Abbreviations: CI, confidence interval; nr, not reported; RR, relative risk

Evidence from studies published since the key systematic review

The key systematic review and meta-analysis published by Moskal *et al* searched the literature to 2005. Two studies published from 2005 onwards were identified. Based on a review of the abstracts from these studies (**Table 12**), the newer evidence is consistent with the Moskal review, finding an increased risk of cancers of the colon and rectum with alcohol consumption compared with abstinence.

Table 20 Brief summary of newer studies of alcohol consumption and risk of cancers of the colon and rectum

Cancer type	Author	Study type	Country	Participants	Findings in relation to cancer risk
Colon & rectal	Bongaerts *et al*, 2006	cohort	Netherlands	120,852 men and women; 4,076 complete dataset with 578 cases	Increased risk with alcohol intake with and without a K-ras mutation in men and women
Colon & rectal	Tsong *et al*, 2007	cohort	Singapore	63,257 middle-aged and older Chinese men and women with 845 cases	Increased risk with high alcohol intake

B.3.5. Alcohol consumption and liver cancer

Risk of liver cancer is thought to be affected by synergistic interactions between alcohol and tobacco, and between alcohol and hepatitis B or C virus (IARC, 1988). The most probable mechanism of alcohol-related liver carcinogenicity is through development of liver cirrhosis, although other events such as changes in hepatic metabolism of carcinogens may also play a role (Boffetta and Hashibe, 2006). Cirrhosis and other liver diseases often occur before evidence of cancer, and thus the effect of

alcohol consumption on the risk of liver cancer is difficult to quantify because patients with these disorders generally reduce their alcohol intake (Bagnardi *et al*, 2001a).

Evidence from key systematic review

There is convincing evidence that heavy alcohol consumption increases the risk of hepatocellular carcinoma. A comprehensive systematic review and meta-analysis of the relationship between alcohol intake and risk of liver cancer was reported by Bagnardi *et al* (2001a). This review included case-control and cohort studies that considered at least three levels of alcohol consumption. Twenty studies were included in total, including three cohort and 17 case-control studies, with a total of 2,294 cases. The results of the meta-analysis show a direct association between risk of liver cancer and alcohol intake, with a 1.17 times increase in risk for alcohol intake of 25 g per day and a 1.86 times increase in risk for heavy drinkers, defined as consumption of 100 g ethanol a day (**Table 21**).

Table 21 Alcohol consumption and risk of liver cancer: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Liver	20 (2,294)	1.17 (1.11, 1.23)	1.36 (1.23, 1.51)	1.86 (1.53, 2.27)
Males	10 (949)	1.28 (1.13, 1.45)	1.51 (1.27, 2.10)	1.62 (1.18, 2.24)
Females	3 (231)	1.97 (1.30, 3.00)	3.57 (1.56, 8.21)	9.15 (1.73, 48.41)

Abbreviations: CI, confidence interval; RR, relative risk

Significant heterogeneity was noted amongst the included studies ($P< 0.05$). The authors explored the effect of gender in modifying the effect of alcohol intake and found a statistically significant ($P< 0.05$) effect of gender, with markedly higher risks in women (ie, a 9.15-times increase in risk with heavy consumption in women compared with a 1.62-times increase in risk with heavy consumption in men; **Table 21**). However, the wide confidence interval around the risk estimate for women reflects the limited data from which the estimate was derived (ie, only three studies involving 231 cases). The effect of smoking adjustment on risk of liver cancer was not examined.

The Bagnardi *et al* (2001a) review made no attempt to assess whether part of the heterogeneity could be explained by the quality of the included studies. However, a subsequent meta-analysis from the same authors was conducted with only those studies that were considered by the authors to be of high quality, based on study design, data collection methods for alcohol consumption, and data analysis (Corrao *et al*, 2004). Ten studies (two cohort and eight case-control, with a total of 1,321 cases) were selected for inclusion in the meta-analysis. The results were remarkably similar to that of the earlier comprehensive meta-analysis reported by Bagnardi *et al* (2001a), with a 1.81-times increase in risk of liver cancer for heavy drinkers, defined as consumption of 100 g of ethanol a day, and no evidence of a

threshold effect (**Table 22**). This review also showed a 27-times increased risk of liver cirrhosis in heavy drinkers (Corrao *et al*, 2004).

Table 22 Alcohol consumption and risk of liver cancer: meta-analyses from Corrao et al (2004)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Liver	10 (1,321)	1.19 (1.12, 1.27)	1.40 (1.25, 1.56)	1.81 (1.50, 2.19)

Abbreviations: CI, confidence interval; RR, relative risk

Evidence from studies published since the key systematic review

A number of primary studies investigating the association between alcohol consumption and risk of liver cancer have been published since the key systematic review by Bagnardi *et al* (**Table 23**). All but two of the newer studies were Japanese. Based on a review of the abstracts from these studies (**Table 23**), the newer evidence is consistent with the Bagnardi review, showing a positive association between alcohol consumption and risk of liver cancer.

Table 23 Brief summary of newer studies of alcohol consumption and risk of liver cancer, by year of publication

Cancer	Author	Study type	Country	Participants	Findings in relation to cancer risk
liver (HCC)	Chira *et al*, 2000	case-control	Romania	50 cases & 100 hospital controls	Increased risk in HCV+ alcoholics compared with mild intake
liver (HCC)	Fukushima *et al*, 2006	case-control	Japan	73 cases & 253 controls	No association between lifetime alcohol consumption and HCV-related HCC
liver (HCC)	Ogimoto *et al*, 2004	cohort	Japan	66,974 men & women. Cases (deaths) not reported	Increased risk with alcohol intake
liver (HCC)	Sakamoto *et al*, 2006	case-control	Japan	209 cases & 275 hospital controls & 381 controls with chronic liver disease	Increased risk with high consumption
liver (HCC)	Takeshita *et al*, 2000	case-control	Japan	102 cases and 125 controls (men & women)	Increased risk with higher cumulative alcohol consumption but not ADH2 or ALDH2 genotypes
liver (HCC)	Wang *et al*, 2003	cohort	Taiwan	11,837 men with 115 cases	Increased risk with alcohol consumption

Abbreviations: HCC, hepatocellular carcinoma

B.3.6. Alcohol consumption and pancreatic cancer

The available evidence for an association between pancreatic cancer and alcohol consumption is not convincing. However, if such an association exists, the most likely mechanism is through development of chronic pancreatitis as a result of alcohol consumption (Boffetta and Hashibe, 2006). In those studies that have reported an association between alcohol intake and risk of pancreatic cancer, residual

confounding due to tobacco cannot be ruled out since tobacco smoking is a strong risk factor for pancreatic cancer.

Evidence from key systematic review

Bagnardi *et al* (2001a) conducted a comprehensive systematic review and meta-analysis of the relationship between alcohol intake and risk of pancreatic cancer. The meta-analysis included cohort and case-control studies that considered at least three levels of alcohol consumption. Seventeen studies (four cohort and 13 case-control studies with a total of 2,524 cases) were included.

The results of the meta-analysis showed no significant association between alcohol and pancreatic cancer. The pooled RR was 0.98 for 25 g alcohol per day and 1.18 for 100 g alcohol per day (**Table 24**), but even at the highest level this failed to reach statistical significance.

Table 24 Alcohol consumption and risk of pancreatic cancer: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Pancreatic	17 (2,524)	0.98 (0.90, 1.05)	1.05 (0.93, 1.18)	1.18 (0.94, 1.49)

Abbreviations: CI, confidence interval; RR, relative risk

Amongst the included studies, significant heterogeneity was noted ($P< 0.05$). No attempt was made to assess the quality of the included studies. There was no evidence of a gender effect in modifying the effect of alcohol. Although tobacco smoking has been reported to be a risk factor for pancreatic cancer, the effect of smoking adjustment on risk of pancreatic cancer was not examined. It is not stated whether the risk estimates reported in the individual studies were adjusted for tobacco.

Evidence from studies published since the key systematic review

A small number of primary studies have been published since the key systematic review by Bagnardi *et al* (**Table 25**). The newer studies supported the findings reported by Bagnardi *et al*, showing no association between alcohol consumption and risk of pancreatic cancer.

Table 25 Brief summary of newer studies of alcohol consumption and risk of pancreatic cancer

Author	Study type	Country	Participants	Findings in relation to cancer risk
Villeneuve *et al*, 2000	case-control	Canada	583 cases & 4,813 controls	No association with alcohol intake
Lin *et al*, 2002	cohort	Japan	110,792 men & women with 225 pancreatic cancer deaths	No association with alcohol intake

B.3.7. Alcohol consumption and lung cancer

Lung cancer accounts for approximately 9% of all cancers in NSW (Tracey *et al*, 2006). Although an association between alcohol drinking and lung cancer risk has been reported in the literature, the relationship is difficult to reliably interpret because of the confounding effects of smoking. There is a substantial body of evidence indicating that cigarette smoking is a strong risk factor for lung cancer (IARC, 2002), and in many countries smoking is highly correlated with alcohol consumption (Pohjanpa *et al*, 1997).

Evidence from key systematic reviews

A comprehensive meta-analysis was conducted by Korte *et al* (2002) with the purpose of reviewing quantitatively the epidemiologic literature on the relation between alcohol consumption and lung cancer, and assessing the role that residual confounding by cigarette smoking could have played in producing the observed associations. The authors concluded that current evidence does not support an association between alcohol consumption and lung cancer, and that confounding by cigarette smoking is responsible for the observed associations. However, the authors were unable to exclude the possibility of a relation between heavy alcohol consumption (classified as five or more drinks per day) and an increased risk of lung cancer.

Korte and colleagues identified 12 cohort studies with 458,359 cases and 11 case-control studies with 11,199 cases. Separate meta-analyses were conducted for case-control and cohort studies, using only the results from the highest alcohol consumption group presented in each study. For cohort studies, the pooled unadjusted RR in relation to non-drinkers was 1.42 (95% CI 1.16-1.73) for overall consumption (using data from the highest alcohol consumption group reported in each study), while the pooled smoking-adjusted RR was attenuated to 1.19 (95% CI 1.11-1.29) (**Table 26**). For case-control studies, the pooled unadjusted OR was 2.18 (95% CI 1.68-2.84) for overall consumption, while the pooled smoking-adjusted OR was 1.39 (95% CI 1.06-1.83) (**Table 26**).

Additionally, meta-analyses were conducted for each of four ethanol consumption groups: 1-499 g/month, 500-999 g/month, 1,000-1,999 g/month, and ≥ 2,000 g/month (roughly equivalent to 1-16 g/day, 16-33 g/day, 33-66 g/day, >66 g/day), with and without adjustment for smoking. In cohort studies, the unadjusted RR was close to unity for low and intermediate alcohol consumption groups (**Table 26**). For consumption in the highest category (≥ 2,000 g/month or approximately seven drinks per day by Australian standards) the unadjusted RR increased to 2.10 (95% CI 1.45-3.05), based on data from only one study. Similarly, results from cohort studies adjusted for smoking showed an increased risk only in the highest consumption category, with an RR of 1.53 (95% CI 1.04-2.25).

Table 26 Alcohol consumption and risk of lung cancer: meta-analyses from Korte et al (2002)

Ethanol consumption by study type	Unadjusted for smoking		Adjusted for smoking	
	# studies	Pooled RR/OR (95% CI)	# studies	Pooled RR/OR (95% CI)
Cohort studies				
1-499 g/month	5	1.08 (0.77, 1.52)	5	0.98 (0.79, 1.21)
500-999 g/month	3	0.93 (0.81, 1.07)	3	0.92 (0.81, 1.04)
1,000-1,999 g/month	3	1.14 (0.89, 1.46)	3	1.04 (0.88, 1.22)
≥2,000 g/month	1	2.10 (1.45, 3.05)	1	1.53 (1.04, 2.25)
Overall [a]	8	1.42 (1.16, 1.73)	11	1.19 (1.11, 1.29)
Including CPS studies [b]				
1-499 g/month	7	1.20 (1.04, 1.39)	7	0.95 (0.87, 1.04)
500-999 g/month	5	1.38 (1.07, 1.77)	5	1.00 (0.94, 1.07)
1,000-1,999 g/month	5	1.84 (1.33, 2.54)	5	1.17 (1.02, 1.33)
≥2,000 g/month	3	2.64 (2.21, 3.15)	3	1.35 (1.16, 1.58)
Case-control studies				
1-499 g/month	3	1.07 (0.63, 1.80)	3	0.63 (0.51, 0.78)
500-999 g/month	5	1.96 (1.48, 2.62)	5	1.30 (0.98, 1.70)
1,000-1,999 g/month	2	2.52 (2.01, 3.15)	2	1.13 (0.46, 2.75)
≥2,000 g/month	1	3.57 (2.62, 4.88)	1	1.86 (1.39, 2.49)
Overall [a]	10	2.18 (1.68, 2.84)	7	1.39 (1.06, 1.83)
Population controls				
1-499 g/month	-	nr	3	0.60 (0.40, 0.88)
500-999 g/month	-	nr	4	0.96 (0.52, 1.81)
1,000-1,999 g/month	-	nr	1	0.68 (0.33, 1.40)
≥2,000 g/month	-	nr	0	-
Overall [a]	-	nr	4	1.09 (0.63, 1.88)
Hospital controls				
1-499 g/month	-	nr	2	0.97 (0.40, 2.34)
500-999 g/month	-	nr	2	1.35 (0.99, 1.84)
1,000-1,999 g/month	-	nr	1	1.70 (1.09, 2.66)
≥2,000 g/month	-	nr	2	1.82 (1.41, 2.35)
Overall [a]	-	nr	3	1.69 (1.35, 2.12)

Abbreviations: CI, confidence interval; CPS, Cancer Prevention Study; nr, not reported; OR, odds ratio; RR, relative risk
NOTE 1: Dose-specific results use only studies with both adjusted and unadjusted results (ie, the same studies are shown at each dose level).
NOTE 2: 1-499 g/month = < 2 drinks/day, 500-999 g/month = >1 to < 4 drinks/day, 1,000-1,999 g/month = > 3 to < 7 drinks/day, ≥ 2,000 g/month = >6 drinks/day.
[a] Overall results use all available studies, based on the highest alcohol consumption group from each study.
[b] The updated meta-analysis includes results from two previously unpublished cohort studies from the American Cancer Society (CPS I and CPS II).

These results should be interpreted with caution because the highest consumption category in any study may be the most vulnerable to residual confounding within that category. Furthermore, very few studies presented data on persons who consumed more than five drinks per day, which limits the ability to draw clear conclusions about risk. When data from two large unpublished cohort studies conducted by the American Cancer Society were included in the analysis, the unadjusted associations were somewhat stronger, ranging up to 2.64 (95% CI 2.21-3.15) in the highest alcohol exposure group (**Table 26**). However, the updated pooled smoking-adjusted associated was slightly weaker in the highest alcohol consumption category (RR 1.35, 95% CI 1.16-1.58).

For case-control studies, unadjusted results showed a notable increase in lung cancer risk beginning at lower levels of alcohol intake than in cohort studies. Whilst alcohol drinkers in the lowest consumption category had no increased risk relative to non-drinkers, the OR for the highest category was 3.57 (95% CI 2.62-4.88), based on one study (**Table 26**). After adjustment for smoking, these results were attenuated and showed a substantial risk increase only in the highest category (OR 1.86, 95% CI 1.39-2.49).

Because of the potential differences between hospital-based and population-based case-control studies in estimating etiologic relations involving alcohol and tobacco, smoking-adjusted results were analysed separately for each study design. Overall, hospital-based case-control studies showed a dose-response relationship between alcohol intake and risk of lung cancer whilst population-based case-control studies provided no evidence for an association (**Table 26**). However, the third and fourth consumption categories were informed by data from one and no population-based case-control studies, respectively.

The authors also examined the risk of lung cancer in two types of presumed excessive drinkers: brewery industry workers and alcoholics. The studies of brewery workers (three studies in total) showed only a very slight excess risk of lung cancer, with a pooled RR of 1.17 (95% CI 0.99-1.39). The studies of alcoholics (12 studies in total) showed a substantial increase in lung cancer risk in relation to general population rates, with a pooled RR of 1.99 (95% CI 1.66-2.39). Neither group of studies were adjusted for differences in smoking habits between the study populations and the comparison populations. Under a range of assumptions, the pooled risk estimate from the studies of alcoholics was then used to simulate control for smoking. The smoking-adjusted RRs showed that uncontrolled confounding by smoking may be responsible for the observed excess of lung cancer among alcoholics relative to the general population.

In additional sensitivity analyses, the authors conducted simulations for misclassification of drinking and smoking status. These analyses indicated that strong misclassification of smoking status could produce an elevated smoking-adjusted risk estimate. Data were also examined from six studies (four case-control and two cohort) that provided data for non-smokers. Overall, the authors concluded that evidence from these trials is inconsistent and provides no strong evidence for an association between alcohol consumption and risk of lung cancer.

It is noteworthy that a systematic review and meta-analysis conducted by Bagnardi *et al* (2001a) also found no significant or consistent relation between alcohol intake and risk of lung cancer. These conclusions were based on a meta-analysis of six studies (three cohort and three case-control). The authors found that any observed trend in association between alcohol intake and risk of lung cancer

was appreciably modified when an allowance was made for tobacco (**Table 27**). There was no evidence of a significant gender effect.

Table 27 Alcohol consumption and risk of lung cancer: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Lung	6 (2,314)	1.02 (1.00, 1.04)	1.04 (1.00, 1.08)	1.08 (1.00, 1.18)
Smoking-unadjusted	nr	1.58 (1.12, 2.24)	2.50 (1.25, 5.01)	6.30 (1.57, 25.18)
Smoking-adjusted	nr	1.01 (0.99, 1.04)	1.03 (0.99, 1.08)	1.07 (0.98, 1.17)

Abbreviations: CI, confidence interval; nr, not reported; RR, relative risk

The Korte and Bagnardi publications did not refer to the effect of passive smoke exposure as a potential source of residual confounding. It is unlikely that many of the primary studies included in the meta-analyses actually collected information on environmental exposure to tobacco. Indeed, Freudenheim *et al* (2005) conducted a pooled analysis of seven cohort studies and stated that only one of the studies, the Netherlands Cohort study, included a detailed assessment of passive smoking. In their discussion, Freudenheim and colleagues postulated that the group of non-smokers who were included in the highest category of alcohol consumption might have heavier exposure to smoke if they drank in smoke-filled environments. However, they concluded that passive smoke exposure is unlikely to explain an association of the magnitude of that observed in men who had never smoked (RR 6.38, 95% CI 2.74-14.90, for ≥ 15 g alcohol per day). By contrast with the findings of increased risk in male never smokers, the authors found little evidence of increased risk in former and current smokers, even in groups that should be similar to the never smokers with respect to lung cancer risk (eg, those who had quit smoking at least ten years before the study, or current smokers of less than 20 cigarettes per day).

Evidence from studies published since the key systematic review

A small number of primary studies have been published since the key systematic review by Korte *et al* (**Table 28**). The findings of these studies are inconsistent, but generally show no clear association between alcohol intake and risk of lung cancer. However, the findings from several studies suggest that red wine consumption may decrease risk. It is unclear from the abstracts whether data were sufficiently adjusted for cigarette smoking. Further research is required to investigate the association between red wine and lung cancer risk.

The largest of the studies was a report from the European Prospective Investigation into Cancer and Nutrition (EPIC; Rohrmann *et al*, 2006). Data was obtained from 478,590 participants. Overall, neither ethanol intake at recruitment nor mean lifelong ethanol intake was significantly associated with lung cancer. However, in comparison with low consumption (0.1-4.9 g alcohol per day), moderate intake (5-

14.9 g alcohol per day) at recruitment was associated with a lower lung cancer risk (HR 0.76, 95% CI 0.63-0.90). A decreased risk was also seen for moderate mean lifelong intake (HR 0.80, 95% CI 0.66-0.97). In contrast, high mean lifelong ethanol intake increased the risk of lung cancer compared with low intake, albeit non-significantly (HR 1.29, 95% CI 0.93-1.74).

Table 28 Brief summary of newer studies of alcohol consumption and risk of lung cancer, by year of publication

Author	Study type	Country	Participants	Findings in relation to cancer risk
Freudenheim *et al*, 2003	case-control	US; + 2 other countries	Not reported	No evidence of risk related to lifetime consumption or alcohol dehydrogenase genotype
Ruano-Ravina *et al*, 2004	case-control	Spain	132 cases & 187 hospital controls	Decreased risk with red wine, increased risk with white wine; no association with beer or spirits
Benedetti *et al*, 2006	2 case-control studies	Canada	699 cases & 507 population controls (men); 1094 cases & 1468 population controls (men and women)	Beer intake increased risk, moderate wine intake decreased risk
Rohrmann *et al*, 2006	cohort	Europe	478,590 participants	Authors concluded no association, but found that moderate alcohol intake is associated with lower risk compared with low intake

B.3.8. Alcohol consumption and prostate cancer

Prostate cancer is the most common cancer in NSW, accounting for 16% of all cancers, and 29% of all cancers in men (Tracey *et al*, 2006). Several studies have found a positive association between alcohol intake and prostate cancer, while others have found no relationship. Due to the high incidence of prostate cancer, further investigation is warranted.

Evidence from key systematic reviews

Dennis *et al* (2000) conducted a comprehensive literature review and meta-analysis to determine the association between alcohol consumption and the risk of prostate cancer. After removing study duplicates and studies that used less than one drink per day as the reference exposure, a total of 33 studies (including six cohort and 27 case-control) were included in the meta-analysis. The authors stratified the data into subgroups based on study design (cohort or case-control), type of control subjects (population, hospital, or benign prostatic hyperplasia controls), and method of data abstraction (reported RR, RR calculated from raw data, or RR pooled from alcohol consumption categories).

The results of the meta-analysis for "never" versus "ever" consumption of alcohol showed no association between alcohol and prostate cancer, with a RR of 1.05 (95% CI 0.98-1.11) (**Table 29**). The pooled estimates varied little by type of study design and no significant heterogeneity was noted in

any of the analyses conducted. By method of abstraction, the highest pooled estimate was 1.08 (95% CI 0.93-1.24).

A potential dose-response relationship with alcohol consumption was examined with data adjusted for covariances of the individual studies (although it made little difference to the estimate or its variance). A linear dose-response was fitted to the 15 studies reporting amount of alcohol consumed, finding a RR of 1.05 (95% CI 0.91-1.20) for each additional drink of alcohol per day, or a RR of 1.21 for four drinks per day (**Table 29**). The authors conducted sensitivity analyses around the number of drinks per day in studies reporting ever consumption. When the average drinks per day consumed in the 15 studies were used to estimate the overall risk for all 33 studies, a RR of 1.02 (95% CI 0.92-1.14) was found for each additional drink of alcohol per day. This estimate did not change appreciably using the minimum and maximum reported number of drinks per day rather than the average from the studies.

One cohort study and 10 case-control studies reported the risk of prostate cancer by type of alcohol consumed. Due to significant heterogeneity amongst studies reporting the consumption of beer and spirits, these meta-analyses were conducted using the random effects method. A positive but non-significant association was seen for all alcohol types. The highest risk was seen in men who drank beer (RR 1.15, 95% CI 0.91-1.46), followed by a RR of 1.10 (95% CI 0.97-1.26) for wine consumption, and 1.04 (95% CI 0.89-1.22) for consumption of spirits (**Table 29**).

Table 29 Alcohol consumption and risk of prostate cancer: meta-analysis from Dennis et al (2000)

Ethanol consumption by study type	# studies	Pooled RR (95% CI)
All studies		
Ever	33	1.05 (0.98, 1.11)
1 drink/day	15	1.05 (0.91, 1.20)
2 drinks/day	15	1.10 (0.96, 1.26)
3 drinks/day	15	1.15 (1.00, 1.32)
4 drinks/day	15	1.21 (1.05, 1.39)
Beer	9	1.15 (0.91, 1.46)
Wine	9	1.10 (0.97, 1.26)
Spirits	10	1.04 (0.89, 1.22)
Cohort studies		
Ever	6	1.00 (0.89, 1.13)
1 drink/day	3	1.02 (0.73, 1.40)
2 drinks/day	3	1.03 (0.75, 1.42)
3 drinks/day	3	1.04 (0.76, 1.45)
4 drinks/day	3	1.06 (0.77, 1.47)
Case-control studies		
Ever	27	1.05 (0.98, 1.13)
Population controls	15	1.05 (0.95, 1.15)
Hospital controls	12	1.08 (0.97, 1.20)
BPH controls only	2	1.30 (0.85, 1.98)
1 drink/day	12	1.06 (0.91, 1.23)
2 drinks/day	12	1.12 (0.96, 1.30)
3 drinks/day	12	1.18 (1.01, 1.37)
4 drinks/day	12	1.24 (1.07, 1.45)

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; RR, relative risk

The lack of a clear association between alcohol consumption and risk of prostate cancer was also noted in a meta-analysis conducted by Bagnardi *et al* (2001a). As mentioned earlier, the authors included case-control and cohort studies that considered at least three levels of alcohol consumption and reported the number of cases and non-cases or estimates of the OR or RR for each exposure level. A total of 11 studies (four cohort and seven case-control, with a total of 4,094 cases) were included in the meta-analysis. The authors noted a weak trend (**Table 30**), but concluded that no significant or consistent relation was observed for cancer of the prostate. There was no evidence of significant heterogeneity between the trials.

Table 30 Alcohol consumption and risk of prostate cancer: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Prostate	11 (4,094)	1.05 (1.00, 1.08)	1.09 (1.02, 1.17)	1.19 (1.03, 1.37)

Abbreviations: CI, confidence interval; RR, relative risk

Evidence from studies published since the key systematic reviews

The literature search conducted in the review by Dennis *et al* (2000) ranged from 1976 to July 1998 and the literature search conducted for the Bagnardi review (2001a) ranged from 1966 to 2000. Several studies investigating the relationship between alcohol consumption and risk of prostate cancer have been published since 2000. As shown in **Table 31**, the findings from these newer studies are inconsistent. One of the larger studies is the Melbourne collaborative cohort study, which examined the relationship between alcohol consumption and prostate cancer risk (Baglietto *et al*, 2006). Baglietto and colleagues reported the results from a prospective cohort of 16,872 Australian men followed-up from 1993 to the end of 2003. In light of limited evidence in the literature to support an association between alcohol consumption and risk of prostate cancer, the study objective was to examine the effect on aggressive and non-aggressive tumours, and the pattern and type of alcohol consumed. A total of 732 incident prostate cancers were identified, including 132 aggressive cases and 53 prostate cancer deaths. Overall, the study showed that alcohol intake was not associated with prostate cancer incidence. Men consuming low alcohol levels (1-19 g/day) had a non-significant reduced incidence of aggressive prostate cancers (hazard ratio 0.67, 95% CI 0.43-1.06) and prostate cancer mortality (hazard ratio 0.56, 95% CI 0.28-1.14). The risk of non-aggressive prostate cancers was close to unity (hazard ratio 1.09, 95% CI 0.85-1.40). The authors found no significant association with pattern of drinking or type of alcoholic beverage consumed.

Several other studies reported an increased risk associated with a particular type of alcoholic beverage (Ellison *et al*, 2000; Sesso *et al*, 2001; Velicer *et al*, 2006). However, there was no consistency in the type of beverage that provided the association. Further investigation of the link between alcohol consumption and prostate cancer, and differential effects of beverage type, is warranted.

Table 31 **Brief summary of newer studies of alcohol consumption and risk of prostate cancer, by year of publication**

Author	Study type	Country	Participants	Findings in relation to cancer risk
Ellison *et al*, 2000	cohort	Canada	3,400 men with 145 cases	No relationship with total alcohol intake; increased risk with wine
Sesso *et al*, 2001	cohort	US	7,612 men with 366 cases	Increased risk with moderate alcohol intake; liquor but not beer or wine increased risk
Barba *et al*, 2004	case-control	US	88 cases & 272 controls	No relationship with alcohol intake; inverse association with total number of drinking years
Crispo *et al*, 2004	case-control	Italy	2,663 cases & 1,451 hospital controls	No association with alcohol intake
Baglietto *et al*, 2006	cohort	Australia	16,872 men with 732 incident cancers	No relationship with alcohol intake or type of beverage
Velicer *et al*, 2006	cohort	US	34,565 men with 816 cases	Increased risk with alcohol consumption, related to white wine intake but not red wine, liquor, or beer.

B.3.9. Alcohol consumption and ovarian cancer

The reported effect of moderate alcohol intake on sex hormone levels and the link with breast cancer risk suggests that alcohol may also influence the risk of ovarian cancer. Previous epidemiological studies have reported a positive, inverse, or null association between alcohol consumption and risk of ovarian cancer. However, many of these studies had limited power to detect an effect because of the small number of cases, particularly for higher levels of alcohol intake (Webb *et al*, 2004).

Evidence from key systematic reviews

The most comprehensive meta-analysis (in terms of total number of included studies) of alcohol intake and the risk of ovarian cancer was undertaken in an Australian publication from Webb *et al* (2004). The study had two components; firstly, the risk of ovarian cancer was evaluated in a case-control study with 696 Australian women with ovarian cancer and 786 population-based controls. A systematic review was then undertaken and the risk estimates from this Australian study were combined with those of other epidemiologic studies. Studies were excluded from the meta-analysis if they did not report a measure of RR and had no control for potential confounders other than age and/or race.

In total, the meta-analyses included seven population-based studies (including the Australian case-control study reported in the same publication) and eight hospital-based studies. Only one of the included studies was a cohort study (population-based). There was statistically significant heterogeneity when the results of all 14 studies identified in the literature search were considered together (P= 0.01). Because of this, the authors chose to analyse the population-based and hospital-based studies separately. Although some variability (P= 0.09) was still observed in the results of the seven population-based studies (including the Australian study), the seven hospital-based studies were reasonably homogenous (P=0.2).

The meta-analysis conducted by Webb *et al* (2004) included only the highest measured level of alcohol intake from each study. Of the individual risk estimates from population-based studies, five were multivariate including smoking. Relative to non-drinkers, the pooled OR for population-based studies was 0.72 (95% CI 0.54-0.97), indicating that women in the highest alcohol groups have a significantly lower risk of ovarian cancer. In contrast, there was no association between alcohol intake and ovarian cancer when the results of the seven hospital-based studies were combined (OR 1.10, 95% CI 0.83-1.44). When the two studies that simply compared drinkers with non-drinkers were excluded, the OR was unchanged (1.10, 95% CI 0.79-1.52). The authors propose that alcohol consumption reported by women who are hospitalised may not accurately reflect that among women in the general population and thus the results of hospital-based studies are difficult to interpret.

The results of the above meta-analysis are not supported by results from a meta-analysis conducted by Bagnardi *et al* (2001a). Case-control and cohort studies were eligible for inclusion in the meta-analysis if they considered at least three levels of alcohol consumption and provided sufficient information to estimate the risks for each exposure level. The authors identified only five studies, all of which were case-control. The total number of cases in these studies was 1,651. No citations or details of the individual studies were provided in the publication and therefore it is not known how many of the included studies were also identified by Webb *et al*. Meta-analysis showed a direct relationship between alcohol intake and risk of ovarian cancer, with a RR of 1.11 (95% CI 1.00-1.24) for 25 g alcohol per day rising to 1.53 (95% CI 1.03-2.32) for 100 g alcohol per day (**Table 32**). There was no evidence of significant heterogeneity amongst the studies.

Table 32 Alcohol consumption and risk of ovarian cancer: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Ovary	5 (1,651)	1.11 (1.00, 1.24)	1.23 (1.01, 1.54)	1.53 (1.03, 2.32)

Abbreviations: CI, confidence interval; RR, relative risk

The Webb meta-analyses found an inverse relationship for studies with population-based but not hospital-based controls. It is possible that all of the studies included in the meta-analysis conducted by Bagnardi *et al* were hospital-based studies. If this is indeed the case, then the results of the two meta-analyses are indeed consistent. However, no details of the included studies are provided in the Bagnardi publication and therefore the matter remains unresolved.

As noted above, the Webb publication included an original epidemiological study in addition to a systematic review and meta-analysis. Webb and colleagues investigated the association between alcohol consumption and risk of ovarian cancer in a case-control study of 696 Australian women with histologically confirmed epithelial ovarian cancer and 786 cancer-free control women selected randomly from the electoral roll (Webb *et al*, 2004). Compared with non-drinkers, consumption of any alcohol was associated with a reduced risk of ovarian cancer with an adjusted OR of 0.71 (95% CI 0.55-0.92). Increasing consumption was associated with a decreasing risk of ovarian cancer, with approximately 50% reduction in risk seen among women who reported an average consumption of two standard drinks compared with non-drinkers (OR 0.49, 95% CI 0.30-0.81). This effect was restricted to wine, with no effect for beer or spirits. The authors concluded that the inverse association with wine may be a consequence of antioxidants and/or phytooestrogens in wine, rather than alcohol itself. There were no statistically significant differences between borderline and invasive cancers or between different histological subtypes. However, the association was significantly stronger among women with a higher level of education, those who had never smoked, and those who used the oral contraceptive pill.

Evidence from studies published since the key systematic reviews

The literature review conducted in the Webb *et al* (2004) publication ranged from August 1990 to December 2003. Several primary studies have been published from 2004 onwards (**Table 33**). Of those with an abstract available, none of the studies showed a positive association between alcohol intake and risk of ovarian cancer. Indeed, the largest of the studies showed a non-significant inverse association with 15 or more grams of alcohol per day.

Table 33 Brief summary of newer studies of alcohol consumption and risk of ovarian cancer, by year of publication

Author	Study type	Country	Participants	Findings in relation to cancer risk
Kelemen *et al*, 2004	cohort	US	27,205 women with 147 cases	Non-significant inverse relationship with alcohol consumption
Schouten *et al*, 2004	cohort	Netherlands	62,573 postmenopausal women with 214 cases	No association with alcohol intake of any type
Larrson *et al*, 2005	not stated	Canada	Not stated	Decreased risk with increased folate, especially in women who consumed alcohol
Pelucchi *et al*, 2005	case-control	Italy	Not reported (no abstract available)	Not reported (no abstract)

B.3.10. Alcohol consumption and stomach cancer

Cancer of the stomach accounts for 2% of all cancers in NSW and is more common in men (Tracey *et al*, 2006). There is inconsistent evidence that alcohol consumption is a risk factor, albeit weak, for the occurrence of stomach cancer.

Evidence from key systematic reviews

A comprehensive systematic review and meta-analysis of the relationship between alcohol intake and risk of stomach cancer was reported by Bagnardi *et al* (2001a). Sixteen studies including two cohort and 14 case-control studies with a total of 4,518 cases were meta-analysed. The results showed a statistically significant relationship between alcohol intake and risk of stomach cancer, although not as strong as that for cancers of the upper aero-digestive tract. The pooled RR was 1.07 for 25 g alcohol per day, 1.15 for 50 g alcohol per day, and 1.32 for 100 g alcohol per day (**Table 34**).

Table 34 Alcohol consumption and risk of stomach cancer: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Stomach	16 (4,518)	1.07 (1.04, 1.10)	1.15 (1.09, 1.22)	1.32 (1.18, 1.49)

Abbreviations: CI, confidence interval; RR, relative risk

Amongst the included studies, significant heterogeneity was noted ($P< 0.05$). The authors made no attempt to assess the quality of the included studies in the 2001 publication or subsequent publications (Corrao *et al*, 2004). There was no evidence of a gender effect in modifying the effect of alcohol. The effect of smoking adjustment on risk of stomach cancer was not examined.

Evidence from studies published since the key systematic reviews

The literature search conducted to identify newer studies published since the key systematic reviews was designed to capture the specific cancers listed within the scope of the current review. Thus, it is not expected that studies investigating the association between alcohol consumption and risk of stomach cancer would have been identified in the search. No studies were located.

B.3.11. Alcohol consumption and other cancers

The literature suggests that alcohol consumption does not increase the risk of melanoma or cancers of the small intestine, gallbladder, cervix, endometrium, bladder, and kidney. Although limited evidence suggests a potential protective effect of alcohol on risk of renal cell carcinoma (Hu *et al*, 2003), further investigation is warranted.

Evidence from key systematic reviews

Bagnardi *et al* (2001a) conducted a comprehensive meta-analysis of the relationship between alcohol intake and risk of cancer at several sites. Case-control and cohort studies published as original articles were included in the meta-analysis. Although six and 11 studies, respectively, were identified for cancers of the endometrium and bladder, only two studies were available to inform the risk estimates for melanoma and cancers of the small intestine, gallbladder, and kidney. The authors identified only one study (case-control) that examined the relationship between alcohol consumption and risk of cervical cancer. This study showed a non-significant inverse relationship between cancer risk and alcohol intake. However, risk estimates for the highest consumption category (100 g/day) was not available from this study. Likewise, risk estimates for the highest consumption category were not available from the individual studies for cancer of the gallbladder. For melanoma, a risk estimate was available only for the lowest consumption category (25 g/day).

The results of the meta-analysis indicate that there is no significant relationship between alcohol consumption and the risk of melanoma or cancers of the small intestine, gallbladder, endometrium, bladder, and kidney (**Table 35**). There was no heterogeneity between studies, except in the case of endometrial cancer which included six studies in the meta-analysis ($P< 0.01$). The authors made no attempt to explore possible sources of heterogeneity. Because of the small number of studies used to inform many of these estimates, further research is warranted to confirm the lack of association.

Table 35 Alcohol consumption and risk of other cancer types: meta-analyses from Bagnardi et al (2001a)

Cancer site	# studies (cases)	Pooled RR (95% CI) associated with alcohol intake		
		25 g/day	50 g/day	100 g/day
Melanoma	2 (708)	0.50 (0.21, 1.10)	-	-
Small intestine	2 (415)	1.02 (0.89, 1.17)	1.04 (0.79, 1.37)	1.08 (0.63, 1.88)
Gallbladder	2 (81)	1.17 (0.73, 1.86)	1.36 (0.54, 3.44)	-
Cervix	1 (242)	0.80 (0.50, 1.27)	0.64 (0.25, 1.60)	-
Endometrium	6 (2,473)	1.05 (0.88, 1.24)	1.09 (0.78, 1.54)	1.20 (0.60, 2.37)
Bladder	11 (5,997)	1.04 (0.99, 1.09)	1.08 (0.98, 1.19)	1.17 (0.97, 1.41)
Kidney	2 (921)	0.88 (0.77, 1.02)	0.79 (0.60, 1.03)	0.62 (0.36, 1.06)

Abbreviations: CI, confidence interval; RR, relative risk

A meta-analysis reported by Mack *et al* (2003) investigated the relationship between alcohol consumption, tea and coffee consumption, and cigarette smoking on risk of thyroid cancer. The authors identified 14 case-control studies, 10 of which were used in the meta-analysis of alcohol intake and risk of thyroid cancer. A crude meta-analysis was conducted for total units of wine and beer consumed per week. There was a significant trend of decreasing thyroid cancer risk with higher levels of alcohol intake ($P = 0.02$), which was eliminated after adjustment for current smoking ($P= 0.12$), indicating that the apparent inverse association was confounded by smoking.

Although no systematic reviews were identified that investigated the association between alcohol consumption and risk of non-Hodgkin lymphoma, it is noteworthy that a pooled analysis showed a decreased risk of NHL with alcohol drinkers compared with non-drinkers. Morton *et al* (2005) pooled data from nine case-control studies (consisting of 8,683 controls and 6,492 cases) participating in the International Lymphoma Epidemiology Consortium. Drinkers had a significantly lower risk of NHL than non-drinkers (RR 0.83, 95% CI 0.76-0.89). There was no consistent dose-response relation between risk of NHL and age at start of alcohol consumption, frequency and duration of alcohol consumption, and total lifetime consumption of alcohol. The inverse association did not vary by beverage type, and the effect was not modified by age, gender, or history of cigarette smoking.

Evidence from studies published since the key systematic reviews

The literature search conducted to identify newer studies published since the key systematic reviews was designed to capture the specific cancers listed within the scope of the review. Thus, it is expected that other less documented cancers in terms of association with alcohol consumption would not have been identified in the search. However, one Swedish study of alcohol and risk of endometrial cancer was found, and showed no increased risk of cancer with alcohol intake (**Table 36**).

Table 36 Brief summary of newer studies of alcohol consumption and risk of endometrial cancer

Author	Study type	Country	Participants	Findings in relation to cancer risk
Weiderpass *et al*, 2001	case-control	Sweden	709 cases & 3,368 population controls	No association with alcohol intake

B.3.12. Conclusions based on review of the evidence

Table 37 summarises the current state of evidence for the association between alcohol consumption and risk of cancer at specific sites, based on the data presented above.

Table 37 Summary of evidence for a link between alcohol and cancer

Cancer site	Relationship between alcohol and cancer	Evidence base
Cancer at any site	No relationship with moderate consumption Increased risk with higher consumption	Convincing
Breast	Increased risk, even with moderate consumption	Convincing
Colon	Increased risk, even with moderate consumption	Convincing
Liver	Increased risk, even with moderate consumption	Convincing
Rectum	Increased risk, even with moderate consumption	Convincing
Stomach	Increased risk, even with moderate consumption	Convincing
Upper aero-digestive tract	Increased risk, even with moderate consumption	Convincing
Cervix	No relationship	Insufficient
Gallbladder	No relationship	Insufficient
Kidney	No relationship	Insufficient
Lung	Possibly increased risk, heavily confounded by smoking	Inconsistent
Melanoma	No relationship	Insufficient
Non-Hodgkin's lymphoma	Possibly decreased risk	Insufficient
Ovary	Conflicting – evidence of increased and decreased risk	Inconsistent
Prostate	No relationship with low consumption Possibly increased risk with heavy consumption	Inconsistent
Small intestine	No relationship	Insufficient
Thyroid	Possibly decreased risk, confounded by smoking	Inadequate
Bladder	No relationship	Convincing
Endometrium	No relationship	Convincing
Pancreas	No relationship	Convincing

NOTE: Moderate consumption is defined as up to 2 alcoholic drinks per day, which is classified as low risk according to 2001 NHMRC guidelines, and the 2007 draft guidelines for public consultation.

There is convincing evidence that alcohol increases the risk of upper aero-digestive tract cancers (oral cavity, pharynx, larynx, oesophagus) and cancers of the breast, colon, rectum, and liver. The evidence suggests that alcohol consumption is not a risk factor for cancers of the pancreas, endometrium, and bladder. The evidence is inconsistent or insufficient for melanoma and cancers of the lung, prostate, small intestine, gallbladder, ovary, cervix, and kidney. The association between alcohol and lung cancer is heavily confounded by tobacco smoking, to the extent that it is difficult to reliably determine the independent effect of alcohol consumption.

For most cancer sites, there is a dose-response relationship with alcohol consumption that persists after adjustment for potential confounders such as age and tobacco, and appears to hold for both men and women. There is no clear evidence of a threshold level below which alcohol intake is safe with regard to risk of cancer. Increased risks were often observed at alcohol intake classified by the NHMRC as responsible or low risk (ie, two alcoholic drinks per day). Unlike cardiovascular disease, there is no consistent evidence that alcohol intake at any level has any protective effect against cancer and there is no evidence whatsoever to support that high risk alcohol consumption has any beneficial effects on health. Although there is some (albeit controversial) evidence to suggest that the detrimental health effects of low levels of alcohol intake may be partially offset by a protective effect of low levels of alcohol intake on cardiovascular disease, not all individuals receive this benefit (see **Section D.2** for further discussion).

C MECHANISMS OF ALCOHOL CARCINOGENICITY

C.1. BIOLOGICAL MECHANISMS

The mechanisms by which alcoholic beverages exert their carcinogenic effect are not fully understood and are likely to differ depending on anatomical site. Possible mechanisms of carcinogenicity of alcoholic drinks are listed in a recent IARC review (Boffetta & Hashibe, 2006), together with a subjective assessment of the strength of the evidence available (**Table 38**).

Table 38 Possible mechanisms of carcinogenicity of alcoholic beverages

Mechanism	Potential target organs
STRONG EVIDENCE	
DNA damage by acetaldehyde	Head & neck, oesophagus, and liver
Increased oestrogen concentration	Breast
MODERATE EVIDENCE	
Solvent for other carcinogens	Head & neck, and oesophagus
Production of reactive-oxygen species and nitrogen species	Liver and others
Changes in folate metabolism	Colon & rectum, breast, and others
WEAK EVIDENCE	
Nutritional deficiencies (eg, in vitamin A)	Head & neck, and others
Reduced immune surveillance	Liver and others
Carcinogenicity of constituents other than ethanol	Head & neck, oesophagus, liver, and others
DNA damage by ethanol	Head & neck, oesophagus, and liver

Adapted from Boffetta & Hashibe (2006)

DNA damage by acetaldehyde

The carcinogenic effect of alcoholic beverages is likely to be, at least for some sites, mediated by acetaldehyde, which is a highly toxic and mutagenic by-product of alcohol metabolism. Ethanol is predominantly metabolised in the liver by alcohol dehydrogenase and also to a lesser degree in the bowel and saliva. Although the liver effectively clears acetaldehyde by converting it to non-reactive acetate, the large intestine and saliva do not clear it as effectively and therefore acetaldehyde can build up to high levels in the gastrointestinal tract (Taylor & Rhem, 2005). Acetaldehyde interferes with DNA synthesis and repair which can consequently result in tumour development. Animal models indicate that acetaldehyde is linked to carcinomas in the mucosa of the upper aero-digestive tract, specifically in the nasal mucosa and larynx (Homann *et al*, 1997; Woutersen *et al*, 1986). In humans, *in vitro* studies have shown that acetaldehyde binds to DNA to form adducts which can result in unregulated cell differentiation and proliferation (Vaca *et al*, 1998), both of which have been implicated in carcinogenesis.

However, the strongest evidence for a causal role of acetaldehyde in alcohol-associated carcinogenesis derives from genetic linkage studies in alcoholics. An increased cancer risk has been shown in

individuals who accumulate acetaldehyde due to variations in the genes coding for enzymes responsible for the generation and detoxification of acetaldehyde. In certain populations of Asian ethnicity, a high percentage of individuals carry a mutation of the acetaldehyde dehydrogenase 2 (ALDH2) gene which is primarily responsible for acetaldehyde oxidation. This results in less acetaldehyde being cleared following ethanol ingestion, and subsequently much higher levels of acetaldehyde building up, resulting in nausea, malaise, and a flushed face. More significant, however, is the substantially higher risk of aero-digestive cancers in this subpopulation (Yokoyama *et al*, 1998). In addition to having high blood acetaldehyde levels, these individuals also have high acetaldehyde levels in their saliva and thus deliver more acetaldehyde directly to the surface mucosa of the upper aero-digestive tract than individuals without the mutation (Väkeväinen *et al*, 2000).

Increased oestrogen concentration

Alcohol drinking affects both male and female reproduction through the adverse regulation of levels of sex hormones and other effects on the cells of the reproductive systems (IARC, 2007). For example, alcohol drinking is associated with decreased menstrual cycle variability, more frequent long cycles, and increased serum and urinary oestrogen metabolites, as well as decreased sex-hormone binding globulin, follicle-stimulating hormone, and luteinising hormone levels (Dumitrescu *et al*, 2005). In breast cancer, alcohol carcinogenicity is thought to be due primarily to increased oestrogen concentrations. Higher oestrogen levels have been shown in women who consume more alcohol (Onland-Moret *et al*, 2005). Moreover, alcohol consumption has been shown to significantly increase serum oestradiol levels (Hines *et al*, 2000).

Three mechanisms have been proposed to be responsible for oestrogen-induced breast carcinogenesis: (i) receptor-mediated hormonal activity promoting cellular proliferation which may lead to carcinogenesis, (ii) activation of cellular pathways involved in drug metabolism, which may lead to increased DNA damage, (iii) induction of chromosomal abnormalities (Russo & Russo, 2004). The first mechanism has gained the widest attention. Ethanol has been shown to increase the activity of oestrogen receptor alpha and also to down-regulate the expression of the tumour-suppressor gene BRCA1, which is a potent inhibitor of oestrogen receptor activity (Fan *et al*, 2000). BRCA1 is widely acknowledged as a breast cancer susceptibility gene; mutations in BRCA1 confer an increased risk for breast cancer and also ovarian cancer (Miki *et al*, 1994; Ford *et al*, 1994). Although several studies have shown that alcohol consumption amongst postmenopausal women is associated with oestrogen and progesterone receptor-positive breast cancers (Enger *et al*, 1999; Li *et al*, 2003), the evidence is conflicting (Gapstur *et al*, 1995).

Solvent for other carcinogens

A number of local mechanisms have been proposed to explain the carcinogenicity of alcohol consumption. Alcoholic beverages may exert a carcinogenic effect by increasing the solubility of carcinogens entering the oral mucosa or perhaps by increasing the permeability of the oral mucosa (Wight & Ogden, 1998). This mechanism would explain the synergistic effect of tobacco smoking and alcohol drinking, whereby alcohol might serve as a solvent for polycyclic aromatic hydrocarbons and similar organic compounds from cigarettes and transport these chemicals to sites they otherwise would not reach. However, this mechanism does not account for the increased risk noted for never-smokers (Boffetta & Hashibe, 2006).

Production of reactive-oxygen species and nitrogen species

One possible mechanism of alcohol-related carcinogenesis is the production of reactive oxygen species and nitrogen species (Molina *et al*, 2003). Chronic alcohol consumption leads to wider tissue distribution and upregulated activity of cytochrome P-4502E1 (CYP2E1), which metabolises ethanol to acetaldehyde. In the liver, the concentration of CYP2E1 is correlated with the generation of reactive oxygen species which can damage cellular proteins, phospholipids, and DNA (Poschl & Seitz, 2004; Hoek & Pastorino, 2002). The induction of CYP2E1 also increases the conversion of various procarcinogens to their ultimate carcinogens (Seitz *et al*, 1998). This mechanism may be particularly relevant with respect to procarcinogens present in tobacco smoke and the well-known synergistic effect of drinking and smoking on upper aero-digestive tract carcinogenesis.

Changes in folate metabolism

Folate deficiency is common in alcoholics (Manari *et al*, 2003). Several mechanisms by which excessive alcohol intake impairs folate intake and bioavailability have been suggested, including decreased folate content of the diet (Manari *et al*, 2003), diminished intestinal absorption (Halsted *et al*, 1971), increased urinary excretion (Russell *et al*, 1983), and cleavage of the folate molecule (Shaw *et al*, 1989). Diminished folate status has been linked to several cancers, including those of the uterine cervix, lung, breast, and colo-rectum (reviewed by Kim, 1999). Although the cellular pathways through which folate inadequacy promotes the likelihood of cancer are not fully delineated, the most likely candidates are impairments in the critical role that folate plays in DNA synthesis, repair and methylation (Choi & Mason, 2002).

Nutritional deficiencies

In heavy drinkers, the entire nutritional status is impaired due to primary and secondary malnutrition (Pöschl & Seitz, 2004). Alcohol consumption influences the disposition and biological efficacy of essential nutrients and dietary factors that are considered cancer protective. Although not fully understood, it is thought that heavy alcohol consumption might lead to nutritional deficiencies through

changes in metabolic pathways, increased urinary excretion, impaired intestinal absorption, or by reduced intake of foods rich in micronutrients (Lieber, 2003). In addition to alcohol's effects on folate (see above), heavy alcohol consumption may also affect the intake, absorption, and metabolism of vitamin B12 and vitamin B6. Furthermore, heavy alcohol users have low serum vitamin A and β-carotene concentrations (Leo & Lieber, 1999), and impaired retinoic acid status (Wang, 2005). Evidence suggests that deficiencies in iron, zinc and selenium may also contribute to cancer development.

Reduced immune surveillance

Chronic alcohol consumption also results in alteration of the immune response (Cook *et al*, 1998), through malnutrition, vitamin deficiencies, established cirrhosis, and alcohol itself. A number of studies have shown that chronic alcoholics are more susceptible to infections and to particular neoplasms, suggesting that alcohol-related alterations of immune surveillance could contribute to the development of cancer (Poschl & Seitz, 2004). Of particular importance is the influence of alcohol on natural killer cells, which are implicated in the control of tumour development and growth. Reduced natural killer cell numbers have been reported in alcoholic cirrhotics (Laso *et al*, 1997) and actively drinking individuals without established alcoholic liver disease (Cook *et al*, 1991).

Carcinogenicity of constituents other than alcohol

It has been suggested that the impurities and contaminants in alcoholic beverages, such as polycyclic aromatic hydrocarbons, nitrosoamines, and mycotoxins, as well as a wide variety of esters, phenols and other compounds derived from interaction between the original plant material and the production processes, contribute to increased cancer risk. If these components are indeed important contributors to carcinogenicity, then risk may vary by type of drink. However, the evidence for a relationship between cancer risk and type of alcoholic beverage is inconsistent (see as mentioned in **Section C.3**).

Other local mechanisms

Other local mechanisms that have been proposed include the direct toxic effect of highly concentrated alcoholic beverages on the epithelium, the altered motility of the oesophagus due to alcohol and enhanced gastro-oesophageal reflux, which may in turn cause inflammation and abnormal transformation of the oesophageal lining (Pöschl & Seitz, 2004), and a decrease in salivary flow leading to a decreased clearing of mucosal surfaces, which could lead to accumulation of carcinogens (Wight & Ogden, 1998).

C.2. INTERACTION WITH TOBACCO

Tobacco products and alcoholic beverages are both classified as Group 1 carcinogens by IARC. It is unsurprising then, that smoking and alcohol have been linked to several types of cancer. However,

separating the effects of alcohol and tobacco remains difficult since heavy drinkers tend to be heavy smokers and *vice versa*. Furthermore, many studies include very few participants who neither drink alcohol nor smoke tobacco. The effect of environmental exposure to tobacco could also be considered a potential source of confounding. In particular, non-smokers with high levels of alcohol consumption might have a heavier exposure to smoke if they drink in smoke-filled environments (Freudenheim *et al*, 2005).

It is widely acknowledged that tobacco is strong risk factor for the development of lung cancer (IARC, 2007). As such, the most important consideration in the interpretation of results from epidemiological studies of the consumption of alcoholic beverages and lung cancer is whether any observed association might be confounded by the effect of smoking. As discussed in **Section B.3.7**, the systematic review conducted by Korte *et al* (2002), found that the positive association between alcohol intake and risk of lung cancer was attenuated by adjustment for smoking, indicating that confounding by cigarette smoking is likely to be responsible for the observed association. Further studies of alcohol consumption in non-smokers are needed to clarify this finding.

Alcohol consumption and tobacco smoking have been causally linked to cancers of the upper aero-digestive tract. The combined effects of alcohol and smoking are greater than additive and are often multiplicative (Menvielle *et al*, 2004). Synergism between alcohol and tobacco was first reported in the 1970's and this synergistic effect has since been estimated to be attributable for over 75% of cancers of the upper aero-digestive tract in developed countries (Blot, 1992). Thus, despite the independent effect that alcohol has on the risk of upper aero-digestive tract cancers, it is the synergistic effect that causes the most harm. One study showed that compared with the risk for non-smoking non-drinkers, the approximate relative risks for developing cancer of the oral cavity are seven times greater for those who use tobacco, six times greater for those who consume alcohol, and 38 times greater for those who use both tobacco and alcohol (Blot, 1992). Another study of laryngeal cancer showed that compared with non-smokers the OR for current smokers was 19.8, current drinkers was 5.9, but for combined alcohol and tobacco consumption was 177 (Talamini *et al*, 2002).

As outlined in **Section C.1**, potential mechanisms for the multiplicative effect of alcohol and tobacco include the ability of alcohol to (i) act as a solvent for other carcinogens, and (ii) increase the permeability of oral mucosa to other carcinogens. This would result in increased uptake of alcohol itself, and of carcinogens, with enhanced systemic effects. Furthermore, the enhanced penetration of carcinogens into proliferating cells may exert a direct mutagenic effect. Indeed, evidence for increased passage of nitrosonornicotine with alcohol has been demonstrated in *in vitro* experiments (IARC, 1988).

C.3. DIFFERENTIAL EFFECT OF DIFFERENT TYPES OF ALCOHOLIC BEVERAGE

For many years now, media have focussed attention on the benefits of wine consumption, particularly that of red wine. This widespread attention has partly been attributed to the illogical phenomenon known as the "French Paradox", which refers to the relative low incidence of coronary heart disease in France despite the relative high intake of saturated fat (Renaud & de Lorgeril, 1992). Wine is assumed to exert its protective effects via inherent secondary plant products with antioxidative, antiproliferative, and antiplatelet properties. However, beer, wine, and spirits each have a characteristic pattern of ingredients which may contribute to the cardioprotective benefit of alcohol consumption, or conversely, to the harmful health effects (Rimm *et al*, 1996).

Analysis of cancer risk by type of alcoholic beverage has not provided consistent results. A few studies have shown a more protective effect from wine and a more harmful effect from beer and spirits. One difficulty in determining an independent effect of a particular alcohol type is that people who drink alcohol tend to drink a variety of alcohol-containing beverages. It is widely accepted that, in general, the beverage associated with the greatest risk of cancer is the most frequently consumed type of alcoholic beverage in each population (Altieri *et al*, 2005; Bagnardi *et al*, 2001b; Burger *et al*, 2004), suggesting that no meaningful difference exists for different types of alcoholic beverages. This finding could potentially be the result of inadequate power to assess uncommon drinks, under-reporting, or misclassification of consumption (Brennan & Boffetta, 2004).

D OTHER ISSUES

D.1. OTHER PUBLIC HEALTH BURDENS ASSOCIATED WITH ALCOHOL CONSUMPTION

Alcohol dependence and excessive alcohol intake are associated with a number of physical and mental health problems that carry significant morbidity and mortality. Although a significant proportion of health problems and deaths are the result of the acute effects of excessive alcohol intake (eg, injuries and deaths due to alcohol-related driving accidents), many more can be attributed to the insidious effects of chronic, excessive consumption and alcohol dependence (Cargiulo, 2007). In addition to an association with particular cancers, excessive alcohol consumption has direct adverse effects on the liver, nervous, and cardiovascular systems. Alcohol dependence is also associated with psychiatric morbidity and an increased risk of suicide. Furthermore, the children of women who consume alcohol while pregnant may be born with permanent disorders that affect mental health and growth. These public health burdens are discussed in brief below.

Risk of injury

Alcohol consumption and alcohol dependence increase the risk of both intentional and accidental injury. Studies have shown no threshold for the risk of injury; the risk starts to increase at relatively low levels of intake and it increases as consumption increases (Cherpitel *et al*, 1995). The risk increases more for people whose level of consumption varies significantly from time to time, and the risk is highest for those who occasionally drink much more than their usual amount (Treno & Holder, 1997).

Less than two standard drinks have been shown to result in cognitive and psychomotor effects that increase risk of injury, such as effects on reaction time, cognitive processing, co-ordination and vigilance (Eckardt *et al* 1998). Drinking alcohol has been associated with risk of injury in many settings, including vehicle and cycling accidents, incidents involving pedestrians, falls, fires, sports and recreational injuries, and violence.

Alcohol can also increase the likelihood and the extent of aggressive behaviour, thereby contributing to risk of injury from violence. Compared with other types of alcohol-related injury, injury related to violence may also be more closely linked to alcohol dependence, (Cherpitel, 1997). Heavy drinking is also a major risk factor for suicide and suicidal behaviour.

Liver disease

In Australia, alcohol consumption is the most common cause of cirrhosis of the liver, and alcoholic cirrhosis is the most common cause of illness and death related to chronic alcohol consumption

(NHMRC, 2001). There is good evidence to show that drinking alcohol over many years can cause cirrhosis in the absence of other causes. However, there is also convincing evidence that alcohol can contribute to the development and course of the cirrhosis in people with haemochromatosis, and increasing evidence that it may be important in conjunction with hepatitis B and C infection. Heavy alcohol intake is associated with the development of steatosis and steatohepatitis, which progresses to fibrosis and ultimately cirrhosis of the liver. Hepatic steatosis is present in as many as 90% of alcoholics (Cargiulo, 2007). Although steatosis will regress with alcohol abstinence, many patients continue drinking and 5% to 15% progress to cirrhosis (Adachi & Brenner, 2005). Meta-analysis of data from over 2,200 cases showed a significantly increased risk of liver cirrhosis starting at the lowest dose of alcohol considered (corresponding to approximately two drinks per day) (Corrao *et al*, 2004).

Neurologic impairment

There is strong evidence that brain damage and related neurologic deficits can be caused from excessive alcohol consumption. Alcohol dependence is associated with decreased regional cerebral blood flow and significant cortical grey matter volume deficits (Pfefferbaum *et al*, 1997; Suzuki *et al*, 2002). People with alcohol dependence may exhibit impairment of working memory, executive functions, visuo-spatial abilities, gait, balance, and cognitive processing of emotional signals (Cargiulo, 2007).

Cardiovascular disease and stroke

Whilst low alcohol consumption is protective against coronary heart disease, heavy alcohol intake is associated with increased risk of coronary heart disease and other cardiovascular disease. A meta-analysis based on data from almost 50,000 cases showed a 13% excess risk of coronary heart disease with heavy intake (100 g/day) (Corrao *et al*, 2004). Consumption of large amounts of alcohol, both on a single occasion ('binge' drinking) and habitually, can also adversely affect the structure and function of the heart. In heavy drinkers and people with alcohol dependence, this damage manifests as cardiomyopathy, disturbances of the heart rhythm, congestive heart failure, and other conditions including sudden death (Puddey *et al*, 1999).

Excessive alcohol consumption is also linked to stroke. Meta-analysis of data from almost 900 cases showed that heavy consumption is associated with a markedly increased risk of ischaemic and haemorrhagic stroke, with a RR of 4.37 and 4.70, respectively (Corrao *et al*, 2004). An important factor contributing to the increased risk of stroke in heavier drinkers may be the effects of heavy drinking in raising blood pressure. It has been shown that high alcohol consumption is associated with significantly higher blood pressure than moderate consumption (Moore *et al*, 1990), and that blood pressure is increased in direct proportion to the amount of alcohol consumed.

Psychiatric conditions

There is consistent and substantial comorbidity between alcohol dependence and other psychiatric conditions, especially mood and anxiety disorders and drug abuse (Cargiulo, 2007). Adults with alcohol dependence have an increased likelihood of having major depression, dysthymia, panic disorder, phobias, mania, hypomania, generalised anxiety disorder, and personality disorders. Alcohol dependence is also associated with illicit drug use and misuse of prescription drugs, and an increased risk of suicide. Of concern, people who are depressed and sometimes drink excessively are at much greater risk of self-harm and suicide, especially if also they drink regularly above guideline levels (NHMRC, 2001). There is also some evidence that alcohol use is associated with poorer outcomes for people suffering from schizophrenia.

Heavy drinking can also aggravate symptoms in people with milder degrees of anxiety and depression. It is clear from the literature that alcohol can provide temporary relief for people experiencing significant anxiety. However, in the longer term, continued drinking over two days or more tends to increase anxiety and depression overall (Kushner *et al*, 2000). Numerous studies have shown that when people with significant alcohol dependence stop drinking entirely, their mood usually worsens over the first few hours and days, but after two to three weeks it is greatly improved (Kushner *et al*, 2000).

Long-term alcohol misuse can also lead to relationship breakdown, social isolation, job loss and money problems. These effects can lead people to drinking more in the hope that it will help them deal with problems, causing a cycle of increasing feelings of anxiety and/or depression and heavy drinking to cope. A recent report from the Australian Government Department of Health and Ageing (Begg *et al*, 2007) indicated that in 2003, mental disorders were responsible for 13.3% of the total burden of disease and injury in Australia, with anxiety & depression (55% of the mental health burden), alcohol abuse (10% of the mental health burden), and personality disorders (9% of the mental health burden) together accounting for almost three-quarters of this burden.

Alcohol and pregnancy

The effects of prenatal alcohol exposure on the physical and nervous system development of the fetus, and on behavioural development in the child, are well acknowledged. The most severe types of harm include gross congenital anomalies and fetal alcohol syndrome which is a specific syndrome of impaired neural development and physical growth and facial abnormalities. The degree of fetal damage is correlated with amount of alcohol intake (Floyd *et al*, 2005). Many children with fetal alcohol syndrome or fetal alcohol spectrum disorders experience social problems, conduct disorders, and mental health problems.

D.2. PROTECTIVE EFFECT IN HEART DISEASE

Although the risk of cancer, cirrhosis of the liver, and alcohol dependence all rise with increasing daily alcohol intake, there is a considerable body of evidence that shows a reduction in the risk of harm with low levels of alcohol consumption (English *et al*, 1995; Holman *et al*, 1996; Corrao *et al*, 2004; Di Castelnuovo *et al*, 2006), due to a specific reduction of ischaemic heart disease and stroke events.

Based on epidemiologic evidence, a J-shaped relationship is seen for alcohol consumption and risk of coronary heart disease (CHD), whereby low to moderate average consumption of alcohol appears to confer a lower risk of CHD incidence and mortality compared to abstinence, whereas heavy average consumption is associated with a risk higher than that for non-drinkers (Corrao *et al*, 2000, 2004). Meta-analysis of 28 high quality prospective cohort studies found that a minimum risk (RR 0.80) was reached at 20 g alcohol per day, a significant protective effect was observed up to 72 g alcohol per day, while a significant increased risk was obtained starting from 89 g alcohol per day (RR 1.05) (Corrao *et al*, 2004). The protective effect of alcohol on CHD shows a pronounced sex effect, with women receiving less protection for a given level of consumption and an earlier upturn of the curve (Corrao *et al*, 2000).

The epidemiological evidence for a protective effect of low to moderate consumption is supported by substantial evidence concerning the biological mechanisms by which a protective effect could be mediated (Rankin, 1994; Svärdsudd, 1998). A publication from the World Health Organization (WHO, Rehm *et al*, 2004) on the global and regional burden of disease outlines seven potential mechanisms: (i) moderate consumption has been linked to favourable lipid profiles, particularly high-density lipoproteins (HDL) which could account for 40-50% of the protective effect of alcohol, (ii) moderate alcohol intake favourably affects coagulation profiles, particularly its effect on platelet aggregation and fibrinolysis, (iii) low to moderate consumption has been shown to favourably affect insulin resistance, (iv) alcohol could protect against CHD through its effect on hormonal profiles, particularly oestrogen, (v) alcohol metabolites may protect against CHD by promoting vasodilatation, (vi) alcohol effects inflammation and through this pathway can influence CHD, and (vii) the antioxidative constituents of alcoholic beverages, especially wine, may mediate a protective effect.

However, the J-shaped relationship between alcohol and health benefits has been questioned in more recent publications. Fillmore *et al* (2006) suggested that the older studies may have suffered from systematic misclassification bias by classifying people who have recently stopped or reduced their drinking as 'abstainers'. This effectively overestimates the health benefits of alcohol consumption, since those who have recently reduced or stopped drinking alcohol may have done so because of alcohol-related ill health. When meta-analyses were conducted on only those studies free from

misclassification biases, the authors found no significant cardioprotective or all-cause associations (Fillmore *et al*, 2006).

However, the findings reported by Fillmore and colleagues are inconsistent with those of a recent prospective cohort study that accounted for systematic misclassification of intake (Harriss *et al*, 2007). The Melbourne study investigated the relationship between alcohol intake and mortality due to CHD and cardiovascular disease (CVD) in 38,200 volunteers aged 40-69 years at baseline with a mean follow-up of 11.4 years. The study found that usual daily alcohol intake was associated with reduced CVD and CHD mortality for women but not men. Moreover, there was an inverse association between drinking frequency and CVD and CHD death which was evident in men but not women.

The relationship between alcohol consumption and risk of death was also investigated according to age and gender by White *et al* (2007). White and colleagues found a direct dose-response relation between alcohol consumption and risk of death in men aged 16-34 years and women aged 16-54 years, whereas the relationship became J- or U-shaped at older ages. The analysis also showed that compared to not drinking, the level at which the relative risk is lowest increases with age, and that the decrease in relative risk with age is more marked in men.

Taken together, the body of evidence suggests that levels of alcohol consumption of the order of one drink per two days may be cardioprotective, but only in older individuals – men over 45 years of age and women after menopause. However, the evidence does not support that people should specifically take up or maintain drinking to obtain health benefits.

D.3. SPECIFIC AUSTRALIAN DATA

D.3.1. Levels of alcohol intake

Levels of alcohol intake in the community are available from the *2006 Report on Adult Health from the New South Wales Population Health Survey*[17], which included questions on the consumption of alcohol. Overall, the survey found that 30.6% of adults do not drink alcohol, 51.9% were classified as low risk, 8.1% were classified as risky, and 9.5% were classified as high risk, as per the 2001 Australian Alcohol Guidelines (for risk of harm in the short-term, see **Table 39**). The proportion of males reporting high risk alcohol drinking was significantly higher than the proportion of females (12.5% versus 6.5%, respectively).

[17] Centre for Epidemiology and Research. *2006 Report on Adult Health from the New South Wales Population Health Survey*. Sydney: NSW Department of Health, 2007.

Table 39 Alcohol drinking by risk, persons aged 16 years and over, NSW, 2006 [a]

Survey response, %	Males	Females	Persons
No drinking	22.4	38.6	30.6
Low risk	55.0	48.8	51.9
Risky	10.2	6.1	8.1
High risk	12.5	6.5	9.5

[a] Estimates are based on 7,904 respondents in NSW. Risk levels for alcohol consumption are based on the 2001 NHMRC Australian Alcohol Guidelines

Source: Centre for Epidemiology and Research. 2006 Report on Adult Health from the New South Wales Population Health Survey. Sydney: NSW Department of Health, 2007.

According to the report, 'any alcohol risk-drinking behaviour' was defined as per Guideline 1 of the 2001 NHMRC Australian Alcohol Guidelines, as one or more of the following: consuming alcohol every day, consuming on average more than 4 if male or 2 if female 'standard drinks' per day, or consuming more than 6 if male or 4 if female 'standard drinks' on any one occasion in the past four weeks. In 2006, just under one third of adults (32.8%) reported any risk drinking behaviour. The proportion of males reporting any risk drinking behaviour was significantly higher than females (37.3% versus 28.4%, respectively). Among males, there was no significant variation across age groups, compared with the overall adult male population. Among females, risk drinking decreased significantly with age. A significantly higher proportion of those aged 16-24 years and 25-34 years, and a significantly lower proportion of those aged 55-64 years, 65-74 years, and over 75 years, undertook any risk drinking behaviour, compared with the overall adult female population.

Encouragingly, the proportion of adults reporting any risk drinking behaviour decreased significantly between 1997 and 2006 in both men (50.6% in 1997 compared with 37.3% in 2006) and women (34.3% in 1997 compared with 28.4% in 2006).

D.3.2. Deaths and illness attributable to alcohol use

In Australia, alcohol consumption is second only to tobacco consumption as a preventable cause of drug-related morbidity and mortality[18]. A recent publication from the Australian Institute of Health and Welfare (AIHW), *The Burden of Disease and Injury in Australia 2003* (Begg *et al*, 2007) calculated alcohol-attributed burden of disease in Australia based on relative risks and population attributable fractions from Ridolfo & Stevenson (2001) for conditions for which there is evidence of causation by alcohol consumption. According to the AIHW report (Begg *et al*, 2007), alcohol has both hazardous and protective effects on health. Whilst alcohol harm was responsible for 3.2% of the total burden of disease and injury in Australia in 2003, it also prevented 0.9% per cent of the total burden, primarily through beneficial effects on ischaemic heart disease, stroke, and other unspecified conditions. Thus, the net impact of alcohol was to contribute to 2.3% of total health burden (**Table 40**). In terms of

[18] Population Health Division. *The health of the people of New South Wales - Report of the Chief Health Officer*. Sydney: NSW Department of Health. Available at: http://www.health.nsw.gov.au/public-health/chorep/atsi/atsi_alc_smo_atsi.htm (accessed 1 November 2007).

deaths, alcohol was attributable for 2.6% of all deaths in Australia in 2003 but prevented 1.8% of all deaths. Thus the net impact of alcohol was to contribute to 0.8% of all deaths (**Table 40**). It is worth noting that the estimate of alcohol attributable harm is likely to be an underestimate because Ridolfo & Stevenson (2001) did not take into consideration the positive association between alcohol and cancers of the colon, rectum, and stomach when calculating population attributable fractions. Furthermore, the 2001 publication by Ridolfo & Stevenson calculated the risk estimate for breast cancer using data obtained from a systematic literature search. All other cancer risk estimates in the Ridolfo & Stevenson publication were taken from an earlier publication by English *et al* (1995) that does not include evidence from a substantial number of newer studies.

Table 40 Deaths and burden attributable to alcohol by specific cause, Australia, 2003

Specific Cause	Deaths		DALYs [a]	
	Number	% of total	Number	% of total
Harm				
Alcohol abuse	918	0.7	34,116	1.3
Suicide & self-inflicted injuries	553	0.4	12,245	0.5
Road traffic accidents	396	0.3	11,121	0.4
Oesophagus cancer	368	0.3	4,594	0.2
Breast cancer	184	0.1	4,152	0.2
Other	1,012	0.8	19,207	0.7
Total attributable harm	*3,430*	*2.6*	*85,435*	*3.2*
Benefit				
Ischaemic heart disease	-1,950	-1.5	-20,659	-0.8
Stroke	-380	-0.3	-3,451	-0.1
Other	-16	0.0	-233	0.0
Total attributable benefit	*-2,346*	*-1.8*	*-24,343*	*-0.9*
Total attributable	**1,084**	**0.8**	**61,091**	**2.3**

[a] The key measure used in this report to measure the total burden of disease and injury is the 'disability-adjusted life year' (DALY). It describes the amount of time lost due to both fatal and non-fatal events ie, years of life lost due to premature death coupled with years of 'healthy' life lost due to disability.
Source: Begg *et al*. The burden of disease and injury in Australia 2003. PHE 82. Canberra: AIHW, 2007

Alcohol abuse, road traffic accidents and suicide contributed two-thirds of the harm attributed to alcohol in 2003, whilst breast cancer and oesophageal cancer each contributed approximately 5% of the total alcohol-attributable burden (Begg *et al*, 2007). In terms of the total burden 'prevented' by alcohol consumption, stroke accounted for 22% (due to beneficial effects of alcohol in females only) and ischaemic heart disease accounted for 77%.

Previous Australian burden studies from the AIHW (Mathers *et al*, 1999, Ridolfo & Stevenson, 2001) reported a substantially higher health benefit due to alcohol compared to the current study ie, an estimated 7,157 deaths being prevented in 1996 compared with only 2,346 deaths being prevented in 2003. This is due to the previous studies underestimating the number of people who abstain from

alcohol or drink less than 0.25 drinks per day. Importantly, the most recent AIHW report states that the protective effect of low alcohol intake on heart disease only becomes apparent after 45 years of age, whereas the harmful effects of alcohol are apparent at all ages (Begg *et al*, 2007). Furthermore, the benefits of alcohol consumption outweigh its harmful effects only in females over the age of 65.

According to the Report of the New South Wales Chief Health Officer [19], alcohol use caused an estimated 1,416 deaths in NSW in 2004 (1,021 males and 395 females). This represents 4.3% and 1.7% of all male and female deaths respectively in NSW. However, the age-adjusted rate of deaths attributable to alcohol has decreased in NSW by 36% between 1985 and 2004, from 31 to 20 deaths per 100,000 population. In contrast, hospitalisations attributable to alcohol have risen by approximately 27% between 1989-90 and 2004-05. Alcohol was attributed to 2.5% and 1.2% of all male and female hospitalisations respectively in NSW in 2004. Again, these estimates are likely to be underestimates because they are based on aetiologic fractions from Ridolfo & Stevenson (2001), which did not consider the association between alcohol and cancers of the colon, rectum, and stomach.

D.3.3. Cancer incidence and mortality attributed to alcohol

The most comprehensive global estimate of the number of deaths caused by alcohol, including cancer-related deaths, was captured as part of WHO's global burden of disease project (Rehm *et al*, 2004). According to the report, malignant neoplasms accounted for 20% of the overall alcohol-attributable mortality burden, second only to unintentional injuries (32%).

According to a report from the AIHW, in 2003 there were an estimated 2,844 new cases of cancer and 1,358 deaths from cancer in Australia attributed to excessive alcohol consumption (AIHW, 2006). Based on aetiological fractions developed by Ridolfo & Stevenson (2001), the age-standardised incidence rate for alcohol-attributed cancer was estimated to be 13.9 per 100,000 persons (12.6 per 100,000 in men and 15.3 per 100,000 in women). The age-standardised mortality rate for alcohol-attributed cancer was estimated to be 6.6 per 100,000 (8.6 per 100,000 in men and 4.9 per 100,000 in women). As above, these are likely to be underestimates because Ridolfo & Stevenson did not consider the association between alcohol consumption and cancers of the colon, rectum, and stomach. Colorectal cancer is the second most common cancer in NSW with 4,517 new cases reported in 2004 (Tracey *et al*, 2006). Thus, even a modest excess risk of colorectal cancer at low levels of alcohol consumption (see **Table 19**) has serious public health implications given that almost 70% of individuals in NSW consume alcohol (**Table 39**).

[19] Population Health Division. The health of the people of New South Wales – Report of the Chief Health Officer. Sydney: NSW Department of Health. Available at http://www.health.nsw.gov.au/public-health/chorep/beh/beh_alcafdthhos.htm. Accessed 31 October 2007.

The AIHW estimated that excessive alcohol consumption may be responsible for 30-50% of all cancers of the upper-respiratory tract and over one-third of all liver cancers (**Table 41**; AIHW, 2006). Although the percentage of breast cancer cases attributable to excessive alcohol consumption is somewhat smaller at 12% (**Table 41**), this actually represents a large number of potentially preventable cases of breast cancer considering that breast cancer is the most common cancer in NSW women (Tracey *et al*, 2006).

Table 41 Cancer site and percentage of cancers attributed to excessive alcohol consumption

Cancers site	Males	Females
Oral cancers	39%	31%
Oesophagus	46%	40%
Larynx	51%	46%
Liver	39%	35%
Female breast cancer	-	12%

NOTE: Derived using aetiological fractions from Ridolfo & Stevenson, 2001
Source: Cancer in Australia: an overview, 2006. AIHW cat. No. CAN 32. Canberra: AIHW.

Alcohol attributable fractions are shown in **Table 42** using the cancers risks shown in **Section B.3**, taken from the meta-analysis by Bagnardi *et al* (2001) for three levels of alcohol intake. Only those cancer types with convincing evidence for a positive and significant association between alcohol intake and cancer risk are shown. In the population who consume an average of two alcoholic drinks per day (considered 'low risk' according to the 2007 draft NHMRC guidelines), it is estimated that alcohol is responsible for 43.2% of cancers of the oral cavity and pharynx, 30.1% of oesophageal cancers in men, 34.2% of oesophageal cancers in women, 22.5% of laryngeal cancers, 23.7% of female breast cancers, 7.4% of cancers of the colon and rectum, 14.5% of liver cancers, and 6.5% of cancers of the stomach. The alcohol attributable fractions for breast and laryngeal cancers are noteably higher than that calculated by the AIHW (Ridolfo & Stevenson, 2001). Ridolfo & Stevenson (2001) did not calculate alcohol attributable fractions for cancer at any site and for cancers of the colon, rectum, and stomach.

Table 42 Alcohol attributable fractions for cancer by alcohol intake levels [a]

Cancers site	Alcohol intake		
	25 g/day	50 g/day	100 g/day
Any site	-	18.0%	47.6%
Oral cavity & pharynx [b]	43.2%	65.2%	83.6%
Oesophagus [c] – males	30.1%	49.5%	71.3%
– females	34.2%	55.4%	77.5%
Larynx [b]	22.5%	40.5%	64.2%
Breast	23.7%	40.1%	63.1%
Colon & rectum	7.4%	15.3%	27.5%
Liver	14.5%	26.5%	46.2%
Stomach	6.5%	13.0%	24.2%

[a] The RR estimates from Bagnardi *et al* (2001) were used to calculate the alcohol attributable fractions for men and women using the following formula (from NHMRC, 2007): AAFi = P × (RRi-1) / [P × (RRi-1) + 1], where i = level of drinking (ie, 25 g, 50 g, 100 g alcohol per day), P = 100% prevalence, assuming all drinkers drink in same quantity, RRi = relative risks for level i.
[b] Tobacco smoking-adjusted risk estimates are used for cancers of the oral cavity & pharynx, and larynx
[c] Risk estimates for oesophageal cancer are shown separately for men and women because of a significant gender effect ($P< 0.05$).

In conclusion, alcohol is one of the most well established causes of cancer and causes a considerable burden of disease in terms of both mortality and morbidity. While the mechanisms of action of alcohol-related risks and benefits await further clarification, the overwhelming public health message is that high daily alcohol intake can have an adverse affect on health and for those who do drink alcohol, it is important to do so in moderation. While the total elimination of alcohol consumption is not realistic, there should be increased community awareness and understanding of the extent and impacts of 'risk drinking behaviour'.

D.4. RESEARCH GAPS AND SCOPE FOR FURTHER RESEARCH

Based on the current review of alcohol consumption and cancer risk, a number of research gaps have been identified that warrant further investigation so that a clearer understanding can be gained of the link between alcohol intake and risk of specific cancers, and the mechanisms underlying such risks. The following areas warrant further investigation:

- Alcohol consumption and risk of cancers of the lung, prostate, ovary, small intestine, gallbladder, cervix, and kidney (Note that the evidence base for these cancers is currently inconsistent and often insufficient)
- Cancer risks associated with lifetime alcohol consumption versus consumption during specific periods
- Patterns of drinking on risk of cancer eg, drinking with meals versus between meals, heavy irregular (binge) drinking
- Role of age at starting and stopping drinking (and starting and stopping smoking for those cancers confounded by tobacco)

- Effect of passive smoke exposure on risk of cancer in alcohol drinkers
- Differential effects by type of alcoholic beverage, particularly a possible decreased risk with red wine
- Risk in different subsites of the upper aero-digestive tract
- Potential mechanisms by which alcohol may affect cancer risk
- Role of folate and other effect modifiers in breast and other cancers (such as colorectal)

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APPENDIX 1: INTERNATIONAL GUIDELINES ON RECOMMENDED UPPER LIMITS OF ALCOHOL CONSUMPTION

Country	Source	Men	Women	Standard Drink	Suggested/Other
Australia	Australian Government Department of Health and Aging [http://www.alcohol.gov.au] National Health and Medical Research Council (NHMRC) http://www.nhmrc.gov.au	No more than 4 standard drinks a day, on average And never more than 6 standard drinks in one day.	No more than 2 standard drinks a day, on average And never more than 4 standard drinks in one day.	10 g	Everyone should have 1 or 2 alcohol-free days every week. Note that the guidelines are currently under review by the NHMRC in collaboration with the Australian Government Department of Health and Ageing. The revised draft, *Australian Alcohol Guidelines for Low-risk Drinking*, is now available for public consultation (the draft advises that both men and women limit their alcohol consumption to 2 standard drinks or less in any one day and states that "not drinking is the safest option" for youths aged under 15 years and women who are pregnant, are planning to become pregnant, or are breastfeeding). Progress on the revised guidelines can be traced at: http://www.nhmrc.gov.au/consult/index.htm.
Austria	Bundesministerium fur Arbeit, Gesundheit und Soziales (Federal Ministry for Labour, Health and Social Affairs) [http://www.bmsg.gv.at/]	24 g pure ethanol per day	16 g pure ethanol per day	10 g	In addition the hazardous limit (unacceptable risk for health consequences) is defined with 40g / 60g alcohol.
Canada	Centre for Addiction & Mental Health	not to exceed 2 units per day (27.2 g/day); not to exceed 14 units per week (190 g/week)	not to exceed 2 units/day (27.2 g/day); not to exceed 9 units per week (12 g/week)	13.6 g	Low risk drinking guidelines: [http://www.camh.net/addiction/pims/pdfs/lowrisk_drinking.pdf] Note: the drinking guidelines do not apply to pregnant women (Source: Centre for Addiction and Mental Health, CAMH)
	Health Canada (Sante Canada)				Moderate drinking means no more than 1 drink a day, and no more than 7 drinks a week. More than 4 drinks on one occasion, or more than 14 drinks a week is a risk to health and safety. If you are pregnant or breast-feeding, avoid alcohol.
	Canadian Cancer Society	<2 drinks/day	<1 drink/day		Research shows that drinking small amounts of alcohol can be good for your heart. However, too much alcohol is known to damage the liver, promote high blood pressure and increase the risk of some types of cancer. Even one drink a day on average can increase the risk of breast cancer. Source: http://www.cancer.ca/ccs/internet/standard/0,3182,3172_1736690838__langId-

Country	Source	Men	Women	Standard Drink	Suggested/Other
					en,00.html
Czech Republic	National Institute of Public Health [http:www.szu.cz]	Less than 24g per day	Less than 16g per day		The recommendations are for adults (over 18), who are healthy (without disease) and not engaged in risky behaviours or taking medication.
Denmark	Sundhedsstyrelsen [National Board of Health (NBH)] [http://www.sst.dk/english/index.asp]	no more than 21 alcohol units (252 g) a week	no more than 14 (168 g) units a week	12 g	The National Board of Health recommends that children under the age of 15 should not drink
Finland	Oy Alko AB (Alko Inc.) [http://www.alko.fi/]	not to exceed 15 units/week (165 g/week)	not to exceed 10 units/week (110 g/week)	11 g	
France	Ministry of Health, Family & Persons with Disablility	not to exceed 20 g/day	not to exceed 20 g/day	12 g/beer, 8 g/wine	National Program for Health & Nutrition (PNNS): La sante vient en mangeant. Those who drink should reduce their consumption. Pregnant women should not drink. Do not drink and drive.
	National Academy of Medicine	not to exceed 5 units/day (60g/day)	not to exceed 3 units/ day (36g/day)	12 g	
Hong Kong	Department of Health & Social Security	not to exceed 3-4 units/day, not to exceed 21units/week	not to exceed 2-3 units/day, not to exceed 14 units/week	1 unit = glass/wine or pint/beer	
Iceland	Alcohol and Drug Abuse Prevention Council				Advice that pregnant women abstain from alcohol during pregnancy and breast feeding since no safe consumption level exists
Indonesia	Ministry of Health				National Dietary Guidelines state: avoid drinking alcoholic beverages.
Ireland	Department of Health	21 units/week (210 g/week)	14 units/week (140 g/week)	10 g	http://www.healthpromotion.ie/topics/alcohol/alcofacts/facts_about_alcohol
Israel	Ministry of Education, Psycological & Counselling Services				Recommended: pregnant women not drink; students not drink more than one unit at a time; avoid alcohol if taking medication.

Country	Source	Men	Women	Standard Drink	Suggested/Other
Italy	Ministry for Agriculture & Forestry and National Institute for Food & Nutrition	Less than 40 g per day	Less than 40 g per day	12g	Nutritional Guidelines: Linee guida per una sana alimentazione italiana The acceptable daily quantity of alcohol is 0.6 g per kilo of body weight. The limit not to be exceeded is 1.0 g per kilo of body weight. If only wine is consumed then the guidelines suggest that less or equal to 450ml (3 glasses) for men and less or equal to 350 ml (2 glasses) for women to be divided between lunch and dinner. Avoid consumption during evolutive age, pregnancy, breast-feeding and reduce it when in old age. Avoid alcohol before driving or when using dangerous machinery, or if undergoing drug therapy. [Legislation: Law Decree 28 Dec. 1998 converted in Law 26 Feb. 1999 n. 39 – Chapter "The aims of Health" pg. 17-18]
Japan	Ministry of Health, Labor & Welfare	1-2 units/day (19.75-39.5 g/day)		19.75 g	
Luxembourg	Ministry of Health				The health authorities promote moderate alcohol consumption without specifying limits of daily or weekly amounts of pure alcohol which should not be exceeded and to refrain from drinking when driving. Children and adolescents less than 16 years of age and young drivers are the main target groups.
The Netherlands	Stichting Verantwoord Alcoholgebruik (Stiva) [www.stiva.nl]	not to exceed 4 units/day (39.6 g/day)	not to exceed 2 units/day (19.8g/day)	9.9 g	Advise not to drink at least 2 days within a week. Avoid alcohol when pregnant, driving or operating machinery and if an adolescent. Women with a low body weight are advised to drink less than the recommended daily limit.
New Zealand	Alcohol Liquor Advisory Council (ALAC)	not to exceed 3 units/day (30 g/day), not to exceed 21units/ week (210 g/week)	not to exceed 2 units/day (20 g/day), not to exceed 14 units/week (140 g/week)	10g	Alcohol-containing drinks are high in energy density and may contribute to weight gain. Have some alcohol-free days each week. To reduce the risk of cancer, no alcohol is recommended. To reduce cardiovascular risk, consume only moderate amounts of alcohol. When serving drinks, ensure non-alcoholic drinks and food are available. Provide non-alcoholic and low-alcohol beverages when serving alcohol. Eat food when drinking alcohol. Restrict or avoid alcohol when driving, when operating machinery or when in the water. The guidelines take into account the protective effect of small amounts of alcohol intake on coronary heart disease, but are not designed for cancer protection. For those who drink alcohol, intake should be kept below the stated levels to help lower the risk of certain cancers and other health and social problems. Research suggests the more alcohol some women drink, the greater their risk of developing breast cancer. Source: http://www.alcohol.org.nz/LowRiskDrinking.aspx
	The Ministry of Health				The "Food and Nutrition Guidelines for Health Pregnant and Breastfeeding Women: A background paper". The guidelines recommend women to avoid drinking alcohol at all during pregnancy unless prescribed during pregnancy and breastfeeding. [http://www.moh.govt.nz/moh.nsf/by+unid/F4F10903136588EFCC25716200123030?Open]
	New Zealand Cancer				Supports the Ministry of Health's *Food and Nutrition Guidelines for Adults*.

Country	Source	Men	Women	Standard Drink	Suggested/Other
	Society				Recommends that non-drinkers do not start using alcohol and drinkers do not increase the amounts they drink to gain the benefit of reduced risk of coronary heart disease. Convincing evidence exists that drinking alcohol increases the risk of developing cancers of the mouth, pharynx, larynx, oesophagus, breast, and liver. As well, alcohol probably increases the risk of developing cancers of the colon and rectum. Further, it is possible that drinking alcohol increases the risk of developing lung cancer. As for most cancers, the risks increase greatly if the person smokes as well. It is possible no level of alcohol consumption is safe with respect to cancer. Any potential benefit from increasing alcohol intake is offset by increased risks of health and social problems, including cancer. Source: http://www.cancernz.org.nz/Uploads/IS_AlcoholandCancer.pdf
Norway	Directorate for Health & Social Welfare				Recommend situational abstinence, such as when driving, during pregnancy, at work or in the company of children and young people.
	Alkokutt http://www.alkokutt.no				Allcokutt suggests: Never to drink on an empty stomach or an empty head. Give a message when someone has got enough. Show respect to people who do not drink alcohol. Remember that women do hold less alcohol than men. Be on guard against drinking-pressure, even among your best friends. Remember time and place where you should not drink alcohol. Never drink alone. Don't drink as an adolescent.
Philippines	Department of Health				National Dietary Guidelines state: for a healthy lifestyle and good nutrition, exercise regularly, do not smoke and avoid drinking alcoholic beverages.
Poland	State Agency for Prevention of Alcohol Related Problems	2 units/day (20 g/day) up to 5 times/week (not to exceed 100 g/week)	1 unit/day (10 g/day) up to 5 times/week (not to exceed 50 g/week)	10 g	Not official guidelines, based on WHO recommendations. Suggest two alcohol free days/week.
Portugal	National Council on Food and Nutrition	2-3 units/day (28-42 g/day)	1-2 units/day (14-28 g/day)	14 g (unofficial)	Based only on wine consumption.
Romania	Ministry of Health	not to exceed 32.5 g beer/day or 20.7 g wine/day	not to exceed 32.5 g beer/day or 20.7 g wine/day		
Singapore	Ministry of Health				National Dietary Guidelines state: Limit alcohol intake to not more than 2 standard drinks a day (about 30 g alcohol).
Slovenia	Institute of Public Health of Slovenia	not to exceed 20 g/day and not to exceed 50 g/drinking occasion	not to exceed 10 g/day and not to exceed 30 g/drinking occasion		
South Africa	South African National Council on Alcoholism & Drug Dependence	not to exceed 21 units/week (252 g/week)	not to exceed 14 units/week (168 g/week)		The government's position is outlined in a brochure titled "Healthy Lifestyles" dated 1995. It calls for using alcohol in moderation and states: "Limit yourself to no more than 2 to 3 drinks a day".

Country	Source	Men	Women	Standard Drink	Suggested/Other
Spain	Ministry of Health and Spanish Institute for the Investigation of Beverage Alcohol	not to exceed 3 units/day (30 g/day)	not to exceed 3 units/day (30 g/day)	10 g	Wine officially considered as an integral part of a Mediterranean diet.
	Basque Country: Department of Health & Social Security	not to exceed 70 g/day	not to exceed 70 g/day		
	Catalonia: Central Authority	not to exceed 4-5 units/day (32-50 g/day)	not to exceed 4-5 units/day (32-50 g/day)	8-10 g	
Sweden	Vetenskapsradet (Swedish Research Council) http://www.vr.se/	not to exceed 20 g/day	not to exceed 20 g/day		Recognised that a moderate alcohol intake may have certain positive medical effects.
	The Swedish National Institute of Public Health (SNIPH)				The SNIPH has created new websites for its project "Responsible alcohol serving". The site has detailed information and material to download for stakeholders such as police, restaurateurs, serving staff, guards and supervision people. [CBA Summary][Source: Alcohol Update - Independent Swedish Newsletter, No 9, 6 October 2006, p4]
Switzerland	Swiss Federal Commission for Alcohol Problems and Institut Suisse de Prevention de l'Alcoolisme et Autre Toxicomanies (Swiss Institute for the Prevention of Alcohol & Drugs Problems)	not to exceed 2 units/day (not to exceed 24 g/day)	not to exceed 2 units/day (not to exceed 24 g/day)	10-12 g	Lists exceptional drinking guidelines: not to exceed 4 units/event, not to exceed 1 unit/hour. No alcohol for youngsters; no alcohol during sports; no alcohol whilst operating machinery or before driving. Females have to be particularly cautious.
Thailand	Ministry of Public Health				National Dietary Guidelines state: avoid or reduce the consumption of alcoholic beverages.
United Arab Emirates	Ministry of Health				No official guidelines. Alcohol available in hotels to guests and visitors. Expatriate residents must possess a liquor permit, available to non-Muslims. Retail outlets sell only to permit holders for personal consumption. Providing alcohol to others is forbidden.
United Kingdom	Department of Health	3-4 units/day (24-32 g/day), not to exceed 21 units/week (168 g/week)	2-3 units/day (16-24 g/day), not to exceed 14 units/week (112 g/week)	8 g	Advises that "pregnant women or women trying to conceive should avoid drinking alcohol. If they do choose to drink, to minimise the risk to the baby, they should not drink more than 1-2 units of alcohol once or twice a week and should not get drunk." Recognizes that moderate drinking for men over 40 and postmenopausal women confer health benefits including lower risk of coronary heart disease, ischemic stroke, gallstones.

Country	Source	Men	Women	Standard Drink	Suggested/Other
	Scottish Executive	3-4 units/day (not to exceed 32 g/day)	2-3 units/day (not to exceed 24 g/day)	8 g	Uses "Sensible Drinking Guidelines" as part of national alcohol strategy.
	Welsh Assembly Government	3-4 units/day	2-3 units/day		If men drink three to four units a day, there will be no significant health risk. Aim to have one or two alcohol-free days a week. For men over 40, drinking one or two units of alcohol a day will help prevent coronary heart disease. If women drink two or three units a day there will be no significant health risk. For women who have been through the menopause, drinking one or two units of alcohol a day will help prevent coronary heart disease. Pregnant women or women trying to conceive should avoid drinking alcohol. Too much drinking can cause cancer of the mouth, throat and gullet. Source: Alcofacts: A guide to sensible drinking. Welsh Assembly Government. June 2007.
United States	Department of Agriculture and Department of Health & Human Services	1-2 units/day (14-28 g/day), not to exceed 14 units/week (196 g/week)	1 unit/day (14 g/day), not to exceed 7units/week (98 g/week)	14 g	Nutrition and your health: Dietary guidelines for Americans (5th ed.) Recognize that moderate drinking may lower the risk of coronary heart disease, among men over 45 and women over 55; Exceeding moderate consumption can raise the risk for accidents, high blood pressure, stroke, violence, suicide, birth defects and certain cancers; A safe level of alcohol intake has not been established for women at any time during pregnancy; Avoid drinking before, or when driving; Consume alcohol with food, to slow absorption.
	National Institute of Alcohol Abuse and Alcoholism (NIAAA)	not to exceed 4 units/day (56 g/day), not to exceed 14 units/week (196 g/week)	not to exceed 3 units/day (42 g/day), not to exceed 7 units/week (98 g/week)	14 g	For most adults, moderate alcohol use causes few if any problems. Source: http://www.niaaa.nih.gov/FAQs/General-English/default.htm#safe_level
	American Heart Association	not to exceed 2 units/day (28 g/day)	not to exceed 1 unit/day (14 g/day)	14 g	AHA Dietary Guidelines Drinking more alcohol increases such dangers as alcoholism, high blood pressure, obesity, stroke, breast cancer, suicide and accidents. Given these and other risks, people should not start drinking if they do not already drink alcohol. Source: Krauss RM, *et al.* Dietary Guidelines for healthy American adults. Circulation 1996; 94:1795-1800.
	American Cancer Society	not to exceed 2 drinks/day	not to exceed 1 drink/day		Alcohol is an established cause of cancers of the mouth, pharynx (throat), larynx (voice box), oesophagus, liver, and breast. Alcohol may also increase the risk of colon and rectum cancer. The combination of alcohol and tobacco increases the risk of some cancers far more than the effect of either drinking or smoking. Regular consumption of even a few drinks per week is associated with an increased risk of breast cancer in women, especially in women who do not get enough folate. Women at high risk of breast cancer may want to consider not drinking any alcohol. Source: http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED

APPENDIX 2: LITERATURE SEARCH FOR SYSTEMATIC REVIEWS

A summary of the search strategies that were employed is presented in Table 43. The aim of the search strategy was to identify published systematic reviews or meta-analyses of alcohol consumption associated with risk of cancer. Therefore, the keywords and descriptors were synonyms for these topics, as shown in **Table 43**. In an effort to exclude narrative reviews that had no systematic basis (numbered in their thousands), the search string for the systematic review section specified that if a publication had been assigned 'review' as a descriptor (rather than 'meta analysis' or 'systematic review', which were automatically captured), it also had to contain the keywords 'meta analysis', 'systemat*' or 'pool*' to be captured by the search. Systematic reviews identified in this way were then considered for inclusion in the current review.

Medline and EMBASE were searched using EMBASE.com, with the Cochrane Library (including DARE) searched separately. Citations and abstracts were downloaded into *Reference Manager Version 10*, and duplicate citations were removed. Following examination of the abstracts and descriptors, all potentially relevant papers were retrieved. Manual searching of the bibliographies of the retrieved papers was undertaken to identify any additional publications not found in the electronic search.

Table 43 Search strategy and results for literature search for systematic reviews

Database (dates covered)	Search terms	Number of articles
EMBASE and Medline (<1966–2007)	**#1 Alcohol terms** 'alcohol consumption'/exp OR alcohol/exp OR 'alcohol abuse'/exp OR alcoholism/exp OR 'alcohol blood level'/exp OR 'drinking behaviour'/exp OR 'alcohol intoxication'/exp OR alcohol*	307,379
(Searched on 17 Jul 2007 using EMBASE.com)	**#2 Cancer terms** 'cancer risk'/exp OR cancer/exp OR 'cancer incidence'/exp OR tumour/exp OR neoplasm/exp [a] OR carcinogen/exp OR 'carcinogenic activity'/exp OR sarcoma/exp OR 'cancer epidemiology'/exp OR tumour* OR tumor* OR cancer* OR neoplas* OR malignan* OR carcino* OR *sarcoma	2,669,881
	#3 Systematic review terms 'meta analysis'/exp OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis' OR 'pooled analysis' OR (review/exp AND ('meta analysis' OR systemat* OR pool*))	80,594
	#4 1 AND 2 AND 3	428
	After removal of duplicates [c]	**422**
DARE (Searched on 7 Aug 2007)	('cancer' or 'carcinoma' or 'carcinogenic' or 'carcinogenesis') and alcohol	**18**
CDSR (Searched on 7 Aug 2007)	('cancer' or 'carcinoma' or 'carcinogenic' or 'carcinogenesis') and alcohol	**191**
Additional sources	Manual searching	**4**
TOTAL		**635**
TOTAL after removal of duplicates		**634**

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects

[a] The descriptor for 'tumor' is located under 'neoplasm' in EMTREE

In the course of examining the retrieved publications, reference lists were checked for additional studies to test the veracity of the literature search conducted for this analysis. Four publications were considered for inclusion based on manual searching (**Table 44**). Three of these papers were ultimately excluded following the retrieval of the full publication (see **Appendix 3** for the reasons for exclusion). A report published by the Australian Institute of Health and Welfare (Ridolfo & Stevenson, 2001) contains a systematic review of alcohol and breast cancer, and was therefore included.

Table 44 Studies identified through manual searching

Citation	Ultimately included or excluded
Ashley MJ, Ferrence R, Room R, Bondy S, Rehm J, and Single E. (1997) Moderate drinking and health. Implications of recent evidence. *Can Fam Physician* 43:687-694.	Excluded
Collaborative group on hormonal factors in breast cancer. (2002) Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. *British Journal of Cancer* 87:1234-1245.	Excluded
Ridolfo B and Stevenson C. The quantification of drug-caused mortality and morbidity in Australia, 1998. 2001. Canberra, Australian Institute of Health and Welfare (Report).	Included
Stoll BA. (1999) Alcohol intake and late-stage promotion of breast cancer. *European Journal of Cancer* 35:1653-1658.	Excluded

Table 45 lists the citations identified by the literature search that were initially considered for inclusion, but subsequently rejected as unsystematic, or incomplete, pooled analyses. These studies were excluded on the basis of being the wrong study type (ie, not a genuine systematic review).

Table 45 Pooled analyses that were excluded after retrieval

Citation	No. of pooled studies
Terry MB, Neugut AI, Bostick RM, Sandler RS, Haile RW, Jacobson JS, Fenoglio-Preiser CM, and Potter JD. (2002) Risk factors for advanced colorectal adenomas: A pooled analysis. *Cancer Epidemiology Biomarkers and Prevention* 11:622-629.	4
Macfarlane GJ, Zheng T, Marshall JR, Boffetta P, Niu S, Brasure J, Merletti F, and Boyle P. (1995) Alcohol, tobacco, diet and the risk of oral cancer: A pooled analysis of three case-control studies. *European Journal of Cancer Part B: Oral Oncology* 31:181-187.	3
Ishikawa A, Kuriyama S, Tsubono Y, Fukao A, Takahashi H, Tachiya H, and Tsuji I. (2006) Smoking, alcohol drinking, green tea consumption and the risk of esophageal cancer in Japanese men. *Journal of Epidemiology* 16:185-192.	2
Morton LM, Zheng T, Holford TR, Holly EA, Chiu BCH, Costantini AS, Stagnaro E, Willett EV, Dal Maso L, Serraino D, Chang ET, Cozen W, Davis S, Severson RK, Bernstein L, Mayne ST, Dee FR, Cerhan JR, and Hartge P. (2005) Alcohol consumption and risk of non-Hodgkin lymphoma: A pooled analysis. *Lancet Oncology* 6:469-476.	9
Castellsague X, Munoz N, De Stefani E, Victora CG, Castelletto R, Rolon PA, and Quintana MJ. (1999) Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. *International Journal of Cancer* 82:657-664.	5
Castellsague X, Munoz N, De Stefani E, Victora CG, Quintana MJ, Castelletto R, and Rolon PA. (2000) Smoking and drinking cessation and risk of esophageal cancer (Spain). *Cancer Causes and Control* 11:813-818.	5
Franceschi S, Levi F, Negri E, Fassina A, and La Vecchia C. (1991) Diet and thyroid cancer: A pooled analysis of	4

Citation	No. of pooled studies
four European case-control studies. *International Journal of Cancer* 48:395-398.	
Bouchardy C, Clavel F, La Vecchia C, Raymond L, and Boyle P. (1990) Alcohol, beer and cancer of the pancreas. International Journal of Cancer 45:842-846.	3
Kurian AW, Balise RR, McGuire V, and Whittemore AS. (2005) Histologic types of epithelial ovarian cancer: Have they different risk factors? *Gynecologic Oncology* 96:520-530.	10
Chen K, Qiu JL, Zhang Y, and Zhao YW. (2003) Meta analysis of risk factors for colorectal cancer. *World Journal of Gastroenterology* 9:1598-1600.	14
Mizoue T, Tanaka K, Tsuji I, Wakai K, Nagata C, Otani T, Inoue M, Shizuka S, Motoki I, Taichi S, Tsugane S, and Yoshitaka T. (2006) Alcohol drinking and colorectal cancer risk: An evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Japanese Journal of Clinical Oncology* 36:582-597.	18
Ogimoto I, Shibata A, and Fukuda K. (2000) World Cancer Research Fund/American Institute of Cancer Research 1997 recommendations: applicability to digestive tract cancer in Japan. *Cancer Causes & Control : CCC* 11:9-23.	43

Table 46 lists a group of publications pertaining to the 'Pooling Project of Prospective Studies of Diet and Cancer', which is an international consortium of cohort studies with the goal of analysing diet and cancer associations using standardised criteria across studies. Although the publications are relevant to alcohol and cancer research, the studies included in each review were identified as part of a project involving the compulsory collection of data on many dietary factors, which would have limited the search results for the purpose of this analysis. These studies were excluded on the basis of having the wrong intervention (ie, diet including alcohol, rather than any alcohol data).

Table 46 Studies pertaining to the 'Pooling Project of Prospective Studies of Diet and Cancer'

Citation	No. of pooled studies
Cho E, Smith-Warner SA, Ritz J, van den Brandt PA, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Holmberg L, Kim DH, Malila N, Miller AB, Pietinen P, Rohan TE, Sellers TA, Speizer FE, Willett WC, Wolk A, and Hunter DJ. (2004) Alcohol Intake and Colorectal Cancer: A Pooled Analysis of 8 Cohort Studies. *Annals of Internal Medicine* 140:603-613+I55.	8
Freudenheim JL, Ritz J, Smith-Warner SA, Albanes D, Bandera EV, van den Brandt PA, Colditz G, Feskanich D, Goldbohm RA, Harnack L, Miller AB, Rimm E, Rohan TE, Sellers TA, Virtamo J, Willett WC, and Hunter DJ. (2005) Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *The American Journal of Clinical Nutrition* 82:657-667.	7
Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Buring JE, Freudenheim JL, Goldbohm RA, Harnack L, Hankinson SE, Larsson SC, Leitzmann M, McCullough ML, Marshall J, Miller AB, Rodriguez C, Rohan TE, Schatzkin A, Schouten LJ, Wolk A, Zhang SM, and Smith-Warner SA. (2006) Alcohol intake and ovarian cancer risk: A pooled analysis of 10 cohort studies. *British Journal of Cancer* 94:757-762.	10
Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, Speizer FE, Willett WC, Wolk A, and Hunter DJ. (1998) Alcohol and breast cancer in women: A pooled analysis of cohort studies. *Journal of the American Medical Association* 279:535-540.	6

Six studies examined the association between polymorphisms (eg, aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH), cytochrome P450 2E1 5'-flanking region (*CYP2E1Pst*I/*Rsa*I)) and cancer (**Table 47**). The use of polymorphisms as surrogates for measuring exposure levels allows the assessment of the causal nature of alcohol exposure. These studies were excluded on the basis of

having the wrong intervention (ie, presence of specific genotypes rather than the consumption of alcohol *per se*).

Table 47 Excluded polymorphism analyses

Citation
Brennan P, Lewis S, Hashibe M, Bell DA, Boffetta P, Bouchardy C, Caporaso N, Chen C, Coutelle C, Diehl SR, Hayes RB, Olshan AF, Schwartzs SM, Sturgis EM, Wei Q, Zavras AI, and Benhamou S. (2004) Pooled Analysis of Alcohol Dehydrogenase Genotypes and Head and Neck Cancer: A HuGE Review. *American Journal of Epidemiology* 159:1-16.
Lewis SJ and Smith GD. (2005) Alcohol, ALDH2, and esophageal cancer: A meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. *Cancer Epidemiology Biomarkers and Prevention* 14:1967-1971.
Boccia S, De Lauretis A, Gianfagna F, van Duijn CM, and Ricciardi G. (2007) CYP2E1PstI/RsaI polymorphism and interaction with tobacco, alcohol and GSTs in gastric cancer susceptibility: A meta-analysis of the literature. *Carcinogenesis* 28:101-106.
Huang WY, Olshan AF, Schwartz SM, Berndt SI, Chen C, Llaca V, Chanock SJ, Fraumeni J, and Hayes RB. (2005) Selected genetic polymorphisms in MGMT, XRCC1, XPD, and XRCC3 and risk of head and neck cancer: A pooled analysis. *Cancer Epidemiology Biomarkers and Prevention* 14:1747-1753.
Wong NACS, Rae F, Simpson KJ, Murray GD, and Harrison DJ. (2000) Genetic polymorphisms of cytochrome p4502E1 and susceptibility to alcoholic liver disease and hepatocellular carcinoma in a white population: A study and literature review, including meta-analysis. *Journal of Clinical Pathology - Molecular Pathology* 53:88-93.
Sun D, Wang X, and Fang J. (2006) Relevance of genetic polymorphism of methylene tetrahydrofolate reductase and susceptibility ot colonic cancer: A meta-analysis. *Chinese Journal of Gastroenterology* 11:516-521.

APPENDIX 3: LIST OF EXCLUDED STUDIES

The literature search for systematic reviews that investigated the association between alcohol consumption and cancer risk identified 634 citations, 31 of which were included and reviewed in **Appendix 2**. A list of the excluded citations is provided below, together with reasons for exclusion.

(1) CME posttest. *Cancer Control* 2003; 10(4):346-348.
Notes: excluded - wrong intervention (ie, alcohol)

(2) Stem cell pacemakers tested. *Exp Rev Cardiovasc Ther* 2004; 2(6):799-801.
Notes: excluded - wrong intervention (ie, alcohol)

(3) Managing empyema in adults. *Drug Ther Bull* 2006; 44(3):17-21.
Notes: excluded - wrong intervention (ie, alcohol)

(4) Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Hypertens Res* 2006; 29(SUPLL.):S1-S102.
Notes: excluded - wrong intervention (ie, alcohol)

(5) Dilemmas in managing Barrett's oesophagus. *Drug Ther Bull* 2006; 44(9):69-72.
Notes: excluded - wrong intervention (ie, alcohol)

(6) -Collaborative-Group-on-Hormonal-Factors-in-Breast-Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies (Structured abstract). *Lancet* 1996; 347:1713-1727.
Notes: Abstract/title: Excluded. Wrong intervention

(7) Abubakar I, Aliyu SH, Arumugam C, Hunter PR, Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. *Abubakar I, Aliyu SH, Arumugam C, Hunter PR, Usman NK Prevention and treatment of cryptosporidiosis in immunocompromised patients Cochrane Database of Systematic Reviews: Reviews 2007 Issue 1 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /1465185* 2007.
Notes: Abstract/title: Excluded. Wrong intervention

(8) Aisner J, Hiponia D, Conley B, Jacobs M, Gray W, Belani CP. Combined modalities in the treatment of head and neck cancers. *Semin Oncol* 1995; 22(3 SUPPL. 6):28-34.
Notes: excluded - wrong intervention (ie, alcohol)

(9) Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Akobeng AK , Gardener E Oral 5 aminosalicylic acid for maintenance of medically induced remission in Crohn's Disease Cochrane Database of Systematic Reviews: Reviews 2005 Issue 1 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 CD003715 pu* 2005.
Notes: Abstract/title: Excluded. Wrong intervention

(10) Alherabi A, Margalani O, Dulguerov P, Fergusson D, Kilty S, Ling F *et al.* Perioperative prophylactic antibiotics in head and neck cancer surgery. *Alherabi A, Margalani O , Dulguerov P, Fergusson D, Kilty S, Ling F , Preston M , Corsten M Perioperative prophylactic antibiotics in head and neck cancer surgery Cochrane Database of Systematic Reviews: Protocols 2005 Issue 3 John Wiley & Sons , Ltd Ch* 2005.
Notes: Abstract/title: Excluded. Wrong intervention

(11) Als NB, Koretz RL, Kjaergard LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. *Als Nielsen B, Koretz RL, Kjaergard LL, Gluud C Branched chain amino acids for hepatic encephalopathy Cochrane Database of Systematic Reviews: Reviews 2003 Issue 1 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 CD001939* 2003.
Notes: Abstract/title: Excluded. Wrong intervention

(12) Als NB, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Als Nielsen B, Gluud LL, Gluud C Benzodiazepine receptor antagonists for hepatic encephalopathy Cochrane Database of Systematic Reviews: Reviews 2004 Issue 2 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 CD002798 pub2* 2004.
Notes: Abstract/title: Excluded. Wrong intervention

(13) Altamura AC, Vismara S, Montresor C, Russo M, Tacchini G. Mortality and suicidal risk in schizophrenia. *Riv Psichiatr* 2002; 37(5):213-224.
Notes: excluded - wrong indication (ie, cancer)

(14) Altieri A, Garavello W, Bosetti C, Gallus S, La Vecchia C. Alcohol consumption and risk of laryngeal cancer. *Oral Oncol* 2005; 41(10):956-965.
Notes: excluded - wrong study type

(15) Ambrosone CB, Shields PG, Freudenheim JL, Hong CC. Re: Commonly studied single-nucleotide polymorphisms and breast cancer: results from the Breast Cancer Association Consortium. *J Natl Cancer Inst* 2007; 99(6):487-489.
Notes: excluded - wrong intervention (ie, alcohol)

(16) Amine EK, Baba NH, Belhadj M, Deurenberg-Yap M, Djazayery A, Forrestre T *et al.* Diet, nutrition and the prevention of chronic diseases. *WHO Tech Rep Ser* 2003; -(916):i-149.
Notes: excluded - wrong intervention (ie, alcohol)

(17) Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. *Andersen BR, Kallehave FL , Andersen HK Antibiotics versus placebo for prevention of postoperative infection after appendicectomy Cochrane Database of Systematic Reviews: Reviews 2005 Issue 3 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /1465185* 2005.
Notes: Abstract/title: Excluded. Wrong intervention

(18) Andrews PJD. Critical care management of acute ischemic stroke. *Curr Opin Crit Care* 2004; 10(2):110-115.
Notes: excluded - wrong intervention (ie, alcohol)

(19) Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. *Angelico F , Burattin M , Alessandri C, Del Ben M , Lirussi F Drugs improving insulin resistance for non alcoholic fatty liver disease and/or non alcoholic steatohepatitis Cochrane Database of Systematic Reviews: Reviews 2007 Issue 1 John Wiley & Sons ,* 2007.
Notes: Abstract/title: Excluded. Wrong intervention

(20) Angus JE, Andriolo R, Bigby M, Goodman S, Jobling R, Williams H. Biologics for chronic plaque psoriasis. *Angus JE , Andriolo R, Bigby M , Goodman S, Jobling R, Williams H Biologics for chronic plaque psoriasis Cochrane Database of Systematic Reviews: Protocols 2006 Issue 4 John Wiley & Sons , Ltd Chichester, UK DOI : 10 1002 /14651858 CD006138 pub2* 2006.
Notes: Abstract/title: Excluded. Wrong intervention

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APPENDIX 4: REVIEW OF IDENTIFIED SYSTEMATIC REVIEWS

KEY AND SUPPORTIVE SYSTEMATIC REVIEWS

Author (year)	Key 2006
Number & type of included studies	98 unique studies (75 retrospective case-control studies [a], 5 prospective case-control studies, and 18 prospective cohort studies) 89 studies were included in the analysis of drinkers vs non-drinkers, 75728 cases 71 studies were included in the analysis of dose-response, 60653 cases
List of included studies	Rohan (1988) Price (1999) Gomes (1995) Rosenberg (1990) Band (2002) Cotterchio (2003) Friedenreich (2001) Lenz (2002) Atalah (2000) Ewertz (1991) Mannisto (2000) Le (1984) Richardson (1991, 1989) Viel (1997) Kropp (2001) Nienhaus (2001) Katsouyanni (1994) Van't Veer (1989) Talamini (1984) Ferraroni (1991, 1993) La Vecchia (1985), Soler (1999), La Vecchia (1989) Ferraroni (1998) Toniolo (1989) Cusimano (1989) Franceschi (1991) Kato (1992) Hirose (1995), Hirose (2003) Kikuchi (1990) Kato (1989) Choi (2003) Sneyd (1991) Adebamowo (1999) Pawlega (1992) Zarridze (1991) Viladiu (1996) Martin-Moreno (1993) Ranstam (1995) Adami (1988) Levi (1996) Morabia (1996) Meara (1989) Meara (1989) Smith (1994) Boice (1995) Vachon (2001)

	Dupont (1989) Byers (1982) Harris (1988) Harvey (1987) O'Connell (1987) Webster (1983), Chu (1989) Young (1989) Nasca (1994, 1990) Miller (1989) Enger (1999), Longnecker (1995) Bowlin (1997) Freudenheim (1995) Harris (1992) Rossing (1996) Longnecker (1995) Brinton (1997), Swanson (1997) Newcomb (1999) Baumgartner (1999) Kabat (1997) Kinney (2000) Zheng (2003) Claus (2001) Wu (2003) Zhu (2003) Gammon (2002) Li (2003) Wrensch (2003) Xiong (2001) Rosenberg (1982) Ronco (1999) Royo-Bordonada (1997) Howe (1991) Friedenreich (1993), Rohan (2000) Hoyer (1992) Tjonneland (2003) van den Brandt (1995) Holmberg (1995) Lahmann (2003) Zhang (1999) Zhang (1999) Simon (1991) Hiatt (1984) Schatzkin (1987) Barrett-Connor (1993) Hiatt (1988) Zhang (1999), Willett (1987), Chen (2002) Graham (1992) Cerhan (1998) Lucas (1998) Potter (1995), Gapstur (1992) Garland (1999) Feigelson (2003) Horn-Ross (2002) Clavel-Chapelon (2002) Smith-Warner (1989)

Population	Not specifically defined.
Exposure	Analysis of drinkers vs non-drinkers was irrespective of consumption (a crude OR was calculated using the number of cases and controls in each consumption band). For analysis of dose-response, alcohol consumption was converted to g/day using conversion factors appropriate to each country. For categorical presentation of alcohol consumption, the midpoint of each consumption band was used to estimate dose-response. For the highest consumption band, a value half the width of the previous interval above the uppermost cut point was assigned.
Control	Non-drinkers. Note that non-drinkers were excluded from the dose-response analysis of the excess risk per 10 g ethanol/day.
Outcomes	OR (95% CI) of incidence of first primary breast cancer associated with drinkers vs non-drinkers; increase in risk of breast cancer incidence amongst drinkers per 10 g ethanol/day; population attributable risk among drinkers of alcohol in the USA and UK.
Statistical considerations	Where estimates of risks were reported for subsets of the study population, an inverse-variance method was used to obtain study-wide risk estimates. An analysis of drinkers vs non-drinkers was carried out using random effects methods to combine log ORs across studies, using a moment estimator of the between study variance. Where a study reported a dose-response analysis only, a crude OR was calculated using the number of cases and controls in each consumption band. Dose-response slopes were calculated for each study using log linear regression and slopes were meta-analysed using random effects methods. Sensitivity analyses were carried out to assess how different quality criteria and control for confounding affected the size of the risk estimate. Studies with potential biases were excluded in the sensitivity analyses. Quality scores were not included as part of the regression analysis or as weights.
Results	According to meta-analysis, OR of the risk of breast cancer associated with drinkers vs non-drinkers 1.11 (95% CI 1.06, 1.17). In studies judged to be of high quality controlled for appropriate confounders (n=19), the OR was 1.22 (95% CI 1.09, 1.37). The combined estimate of excess risk per 10 g/day of ethanol was 12% (95% CI 9, 15%). In studies judged to be of high quality controlled for appropriate confounders (n=33), the excess risk was 10% (95% CI 5, 15%). All analyses showed significant heterogeneity ($P< 0.05$) across studies. Retrospective case-control studies with hospital controls were associated with significantly higher OR estimates than those of community controls ($P< 0.05$). Risk did not differ significantly by beverage type, menopausal status, or nationality. Funnel plots did not indicate any evidence for publication bias. Population attributable risk among drinkers in the USA and UK was estimated to be 1.6% and 6.0%, respectively.
Author's conclusions	This is the largest and most comprehensive meta-analysis to date of the relationship of alcohol and breast cancer and provides a sound basis for guiding public health policy in this area. The epidemiological evidence of a positive association between alcohol consumption and risk of breast cancer is robust to the quality and type of study included, and cannot readily be explained by bias or confounding.
Reviewer's conclusions/ comments	The findings from this comprehensive meta-analysis are robust given the extensive sensitivity analyses conducted.
Quality assessment	A. A specific clinical question was not defined; however, the aim was to provide robust quantitative estimates of the alcohol-breast cancer association to guide public health policy. B. Yes. Included electronic and manual searching between 1 Jan 1966 and 31 Dec 2003, including a search of the grey literature and conference proceedings. C. Yes. Studies were eligible for inclusion if they reported original data, assessed incidence, and considered first primary breast cancer. Publications in any language were considered. Data were abstracted independently by two reviewers. Any discrepancies were referred to a panel for resolution. D. Yes. The same reviewers used a simple scoring system to assess study quality. The scoring system took into account study design issues and control for confounding.

	E. Yes. The study details of individual studies were appropriately summarised. However, the results of individual studies were not. F. Yes. An analysis of drinkers vs non-drinkers was carried out using random effects methods to combine log ORs across studies, using a moment estimator of the between study variance. A pooled RR and 95% CIs associated with alcohol intake was reported. G. Yes. Heterogeneity in results across studies was examined using the Q statistic. Meta-regression with random effects was used to explore heterogeneity according to study type (case-control vs cohort), hospital-based vs community controls in case-control studies, data collection before or after disease onset, menopausal status, and nationality of the study population.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

[a] An additional two studies were identified and used in a sensitivity analysis but were not used in the primary analyses due to overlap of cases with other studies.

Author (year)	Moskal 2006
Number & type of included studies	16 cohort studies (5 reported RR for colorectal cancer, 14 for colon cancer, and 12 for rectal cancer), >6,300 cases
List of included studies	Wakai (2005) Chen (2005) Sanjoaquin (2004) Su & Arab (2004) Wei (2004) Wei (2004) Otani (2003) Shimizu (2003) Pedersen (2003) Harnack (2002) Flood (2002) Singh (1998) Chyou (1996) Glynn (1996) Murata (1996) Giovannucci (1995) Gapstur (1994) Goldbohm (1994) Stemmermann (1990)
Population	Not specifically defined.
Exposure	Highest versus lowest category of alcohol consumption reported in each study. Highest levels of alcohol intake ranged from 154-462 g/week in Asian studies, 15-159 g/week in American studies, and 194-492 g/week in European studies, and from 140-257 g/week in women and 140-462 g/week in men. Dose-response analysis was conducted with 3 exposure categories: 25 g increase/week, 50 g increase/week, 100 g increase/week.
Control	Lowest category of alcohol consumption reported in individual studies. Lowest alcohol category was 'non-drinker' in 11 studies, and various definitions in <1 unit/week, 0-153 g/week, <1 drink/week, <20 g/day, <1 times/week, 0.01-5.3 g/day, 0-0.25 drinks/day, 0.1-4.9 g/day.
Outcomes	RR (95% CI) of incidence of colorectal cancer by anatomical site
Statistical considerations	The maximally adjusted RRs (or ORs) and CIs were extracted from publications. The association of alcohol with colorectal cancer risk was quantified as the weighted mean of the logarithm of RR estimates associated to the highest versus lowest category of alcohol consumption reported. Study-specific dose-response slopes were estimated by relating the logarithm of the RRs for different exposure levels to their corresponding alcohol content, using the method of Greenland & Longnecker (1992). Results were expressed as an increase of 100 g/week of alcohol, corresponding to approximately 5 and 7 drinks in Asia and USA, respectively. Alcohol consumption reported as number of drinks was rescaled using standard alcohol content per drink in the same study population or geographical area. The mid-point of the range of alcohol intake was assigned as the exposure category. When the highest category was open-ended, the width of the interval was assumed to be the same as the preceding category. Heterogeneity was tested using Q-test and Chi-square score, and explored using meta-regression. Random effects models were assumed when there was evidence of heterogeneity.
Results	*Highest vs lowest level of alcohol intake*: Colorectal RR 1.34 (95% CI 0.92, 1.96), men RR 1.73 (95% CI 1.00, 2.98), women RR 0.88 (95% CI 0.61, 1.27) ; heterogeneity $P<0.01$ for all studies, $P<0.05$ for men Colon RR 1.50 (95% CI 1.25, 1.79), men RR 1.64 (95% CI 1.39, 1.93), women RR 1.23 (95% CI 0.00, 1.51) ; heterogeneity $P<0.05$ for all studies Rectum RR 1.63 (95% CI 1.35, 1.97), men RR 1.79 (95% CI 1.38, 2.33), women RR 1.39 (95% CI 0.95, 2.02) ; no heterogeneity Geographical area was a significant source of heterogeneity between studies for colon cancer, with and without adjustment for level of alcohol intake. *Dose-response analysis, for an increase of 100 g alcohol intake per week* : Colorectal RR 1.19 (95% CI 1.14, 1.27), men RR 1.21 (95% CI 1.02, 1.43), women RR 1.05 (95% CI 0.92, 1.20); no heterogeneity

	Colon RR 1.15 (95% CI 1.07, 1.23), men RR 1.18 (95% CI 1.13, 1.24), women RR 1.14 (95% CI 1.00, 1.30) ; heterogeneity *P*<0.001 for all studies Rectum RR 1.15 (95% CI 1.10, 1.21), men RR 1.19 (95% CI 1.12, 1.26), women RR 1.16 (95% CI 0.94, 1.44) ; no heterogeneity *Dose-response analysis, for an increase of 25 g alcohol intake per week* : Colon RR 1.03 (95% CI 1.02, 1.05) Rectum RR 1.04 (95% CI 1.02, 1.05) *Dose-response analysis, for an increase of 50 g alcohol intake per week* : Colon RR 1.07 (95% CI 1.03, 1.11) Rectum RR 1.07 (95% CI 1.05, 1.10)
Author's conclusions	Higher alcohol intake was associated with increased risk of colon and rectal cancer when comparing the highest with the lowest category of alcohol intake. The relationship did not differ significantly by anatomical site (colon, rectum). Geographical area where the study was conducted was identified as a possible source of between-study heterogeneity.
Reviewer's conclusions/ comments	Included only prospective studies which are less vulnerable to selection and recall bias than case-control studies. No analysis was conducted relative to non-drinkers.
Quality assessment	A. A specific clinical question was not defined; however, the aim of the study was 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. B. Yes, but suboptimal. Included search of MEDLINE between 1990 and June 2005, and a manual search of references from the identified articles. C. Yes. Studies were eligible for inclusion if they were prospective cohort studies evaluating the relationship between total alcohol consumption and colorectal cancer risk, were published in English and referenced in MEDLINE, reported colorectal cancer incidence as an endpoint, and provided RR estimates and 95% CIs or enough information for computation of unadjusted variance. For inclusion in the dose-response analysis, studies had to report at least 3 categories of exposure, number of cases and comparison subjects for each category. D. No. The authors made no attempt to assess study quality. E. Yes. The study details of individual studies were appropriately summarised. However the results of individual studies were not. F. Yes. In addition to pooling all identified studies, separate analyses were conducted based on anatomical site, gender, and geographical location of the study. Data were analysed using the random effects model where there was evidence of heterogeneity. A pooled RR and 95% CIs associated with alcohol intake was reported. G. Yes. Random effects models were assumed when there was evidence of heterogeneity. The extent of heterogeneity was quantified using Q-test and I^2 score. Meta-regression was used to explore the influence of tumour site, gender, geographical region, dose of ethanol intake in the highest consumption category, and publication year in the heterogeneity.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

Author (year)	Corrao 2004
Number & type of included studies [a]	Oral cavity & pharynx: 15 studies meta-analysed (1 cohort and 14 cases-control), 4507 cases Oesophagus: 14 studies meta-analysed (1 cohort and 13 case-control), 3233 cases Larynx: 20 studies meta-analysed (all case-control), 3789 cases Colon: 16 studies meta-analysed (12 case-control and 4 cohort), 5360 cases Rectum: 6 studies meta-analysed (4 case-control and 2 cohort), 1420 cases Liver: 10 studies meta-analysed (8 case-control and 2 cohort), 1321 cases Breast: 29 studies meta-analysed (24 case-control and 5 cohort), 32175 cases
List of included studies	Of the included studies, those of high quality score, those reporting estimates for the main risk indicators, or performed with a prospective cohort design, were selected for meta-analysis. Study details were not provided.
Population	Not specifically defined.
Exposure	Only those studies that considered at least 3 levels of alcohol consumption and reported the number of cases and non-cases, and the estimates of the odds ratios or RR for each exposure level were eligible for inclusion. The 3 exposure levels were as follows : 25 g/day (ie, approximately 2 drinks), 50 g/day (ie, approximately 4 drinks), 100 g/day (ie, approximately 8 drinks)
Control	Non-alcohol drinkers.
Outcomes	RR (95% CI) of incidence of particular cancers for selected doses of alcohol intake and for alcohol intake lower than 25 g/day.
Statistical considerations	A family of second-degree models was generated by power transformation of the exposure variable, and the best-fitting model was chosen to summarise the relation of interest. Several meta-regression models were fitted with qualitative characteristics of the studies as covariates. If the qualitative characteristics resulted as significant effect modifiers, studies of higher quality were selected with the aim of yielding more reliable functions. Pooled RR and the corresponding 95% CI were derived from the parameters of the meta-regression models to obtain an estimate of the risk associated with specific doses of alcohol. The consistency of the model-based RR was evaluated with reference studies reporting RR for light consumption (≤25 g/day). Homogeneity of the RR across studies was tested using the Q statistic. Random effects models were used when there was evidence of significant heterogeneity.
Results [a]	Oral cavity & pharynx: 25 g/day RR 1.86 (95% CI 1.76, 1.96); 50 g/day RR 3.11 (95% CI 2.85, 3.39); 100 g/day RR 6.45 (95% CI 5.76, 7.24). Oesophagus: 25 g/day RR 1.39 (95% CI 1.36, 1.42); 50 g/day RR 1.93 (95% CI 1.85, 2.00); 100 g/day RR 3.59 (95% CI 3.34, 3.87). Larynx: 25 g/day RR 1.43 (95% CI 1.38, 1.48); 50 g/day RR 2.02 (95% CI 1.89, 2.16); 100 g/day RR 3.86 (95% CI 3.42, 4.35). Colon: 25 g/day RR 1.05 (95% CI 1.01, 1.09); 50 g/day RR 1.10 (95% CI 1.03, 1.18); 100 g/day RR 1.21 (95% CI 1.05, 1.39). Rectum: 25 g/day RR 1.09 (95% CI 1.08, 1.12); 50 g/day RR 1.19 (95% CI 1.12, 1.24); 100 g/day RR 1.42 (95% CI 1.30, 1.55). Liver: 25 g/day RR 1.19 (95% CI 1.12, 1.27); 50 g/day RR 1.40 (95% CI 1.25, 1.56); 100 g/day RR 1.81 (95% CI 1.50, 2.19). Breast: 25 g/day RR 1.25 (95% CI 1.20, 1.29); 50 g/day RR 1.55 (95% CI 1.44, 1.67); 100 g/day RR 2.41 (95% CI 2.07, 2.80).
Author's conclusions [a]	Strong trends in risk were observed for cancers of the oral cavity & pharynx, oesophagus, and larynx. Less strong relationships were observed for cancers of the colon, rectum, liver, and breast. Significant increased risks were also found for ethanol intake of 25 g/day. The meta-analysis showed no evidence of a threshold effect for any of the cancer sites considered. No citations or details of the individual studies were provided in the publication and therefore it is not known if any of the included studies were Australian.
Reviewer's conclusions/ comments	This evaluation may be more reliable than the Bagnardi *et al* (2001) publications because it considered only those studies of higher quality and those that adjusted for major known risk factors.
Quality assessment	A. A specific clinical question was not defined; however, the objective was to quantify the dose-risk effect of alcohol on 14 major alcohol-related conditions. B. Yes. Included electronic and manual searching to 2000, including a hand-search on the most relevant journals of epidemiology and medicine, and a manual search of published general reviews and meta-analyses on the issue. C. Yes. Studies were included if they were a case-control or cohort study published as an original article, expressed findings as OR or RR, considered at least 3 levels of alcohol consumption,

	reported the number of cases and non-cases, and estimated the OR or RR for each exposure level. The eligibility of each paper was independently determined by two assessors who were blinded to the author's names and affiliations and the results pertaining to alcohol consumption. D. Yes. The same assessors evaluated several characteristics of each study and scored the quality of the studies according to pre-defined criteria. The assessors also evaluated whether each study reported RR adjusted for major known risk factors. Discrepancies between assessors were resolved in conference. E. No. The study details and results of individual studies were not presented. The publication showed aggregated and meta-analysed data only. F. Yes. Regression models were fitted by pre-pooling the results of all included studies, taking into account the correlation between estimates within each study. Random effects models were used when there was evidence of significant heterogeneity. A pooled RR and 95% CIs associated with alcohol intake was reported for each neoplasm/condition of interest. G. Yes. Reasons for heterogeneity were investigated by including as covariates particular qualitative characteristics of the studies. The author's state that they used data from only those studies that met *a priori*-defined quality criteria in order to control for heterogeneity.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

[a] Refers to evaluation of cancer risk only. Note that the publication also evaluated the relationship between alcohol intake and the risk of 8 non-neoplastic conditions.

Author (year)	Webb (2004)
Number & type of included studies	13 studies (6 population-based case-studies, 1 population-based cohort, & 7 hospital-based case-studies) plus 1 Australian population-based case-control study conducted by the authors.
List of included studies	Gwinn (1986) Whittemore (1988) Kushi (1999) Kuper (2000) Goodman (2003) Schouten (2003) Webb (current publication 2004) Hartge (1989) Kato (1989) Polychronpoulou (1993) Nandakuma (1995) Tavani (2001) Yen (2003)
Population	Cases of ovarian cancer
Exposure	Comparison of highest and lowest consumption group ie, highest ranging from > 6 to >21 standard drinks per week across the studies. Two of the included studies compared drinkers (regardless of consumption) with non-drinkers.
Control	Non-drinkers
Outcomes	RR of ovarian cancer for population-based and hospital based studies.
Statistical considerations	Limited details provided. Assumes 1 drink = 12.6 g alcohol. When 95% CIs were not reported they were calculated from the *P*-value, if available, using test-based limits. Due to significant heterogeneity (tested using Chi-square) when all identified studies were meta-analysed, population-based and hospital-based studies were analysed separately. Studies were excluded if they did not control for potential confounders other than age and/or race. Summary ORs were calculated using a random effects model.
Results	For drinkers vs non-drinkers OR 0.72 (95% CI 0.54-0.97) for 7 population-based studies; OR 1.10 (95% CI 0.83-1.44) for 7 hospital-based studies.
Author's conclusions	Combining the results of the Australian case-control study with data from six previous population-based studies resulted in a significant inverse association, due solely to wine consumption, which may be a consequence of antioxidants and/or phytooestrogens in wine rather than the alcohol itself.
Reviewer's conclusions/ comments	Australian study. Publication reports the results of a case-control study, which is then meta-analysed with other studies identified in a literature search. Marked difference in direction of risk from raw data from hospital-based vs population-based studies. No dose-response analysis conducted.
Quality assessment	A. A specific clinical question was not defined; however, the aim of the study was to evaluate the association between alcohol intake and ovarian cancer risk in a large population-based case-control study conducted in Australia, and to bring together all of the published data evaluating the association between alcohol consumption and epithelial ovarian cancer to comprehensively examine the association. B. Yes, but suboptimal. Included search of MEDLINE between 1966 and 2003, and a manual search of references from the identified articles. C. Unclear. Studies were excluded if they did not report RRs for the association between alcohol and ovarian cancer or if they presented only crude or age-adjusted estimates with no control for other potentially important confounders. It is not stated whether more than one reviewer assessed eligibility. D. No. The authors made no attempt to assess study quality. However, they did exclude studies that had no control for confounders other than age and/or race. E. Inadequate. The study details and results of individual studies were provided. However only for highest vs lowest consumption category reported.

	F. Yes. In addition to pooling all identified studies, separate analyses were conducted based on study type – population-based or hospital-based. Data were analysed using the random effects model. A pooled OR and 95% CIs associated with alcohol consumption was reported. G. Yes. The extent of heterogeneity was quantified using Chi-square test. Due to significant heterogeneity for all studies together, the results for population-based and hospital-based studies were examined separately. No significant heterogeneity was noted between the 7 population-based studies and the 7 hospital-based studies.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

Author (year)	Korte 2002
Number & type of included studies	12 cohort studies (8 and 11 of which contributed to the unadjusted and adjusted pooled estimate of the highest alcohol consumption group from each study, respectively), 3521 cases & 458,359 controls 11 case-control studies (10 and 7 of which contributed to the unadjusted and adjusted pooled estimate of the highest alcohol consumption group from each study, respectively), 3926 cases & 11,199 controls 11 studies of alcoholics (12 studies contributed to the pooled estimate) 3 studies of brewery workers (all 3 contributed to the pooled estimate) 2 additional cohort studies conducted by the American Cancer Society
List of included studies	*Studies of alcoholics*: Sundby (1967) Pell and D'Alonzo (1973) Hakulinen (1974) Monson & Lyon (1975) Adelstein & White (1976) Robinette (1979) Schmidt & Popham (1981) Prior (1988) Adami (1992) Tonnesen (1994) Sigvardsson (1996) *Studies of brewery workers*: Dean (1979) Jensen (1979) Carstensen (1990) *Cohort studies*: Klatsky (1981) Kvale (1983) Pollack (1984) Kono (1986) Hirayama (1986) Chow (1992) Doll (1994) Omenn (1996) Yong (1997) Bandera (1997) Woodson (1999) Prescott (1999) *Case-control studies*: Bradshaw & Schonland (1969) Williams & Horm (1977) Herity (1982) Stockwell & Matanoski (1985) Mettlin (1989) Connett (1989) Potter (1992) Bandera (1992) De Stefani (1993) Dosemeci (1997) Carpenter (1998) *Additional cohort studies*: Cancer Prevention Study I (CPS-I) Cancer Prevention Study II CPS-II)
Population	Not specifically defined for analyses of cohort and case-control studies.

	Also meta-analysed studies of two types of presumed excessive drinkers: alcoholics, and brewery industry workers.
Exposure	Ethanol consumption was estimated from each study in g/month (1 drink = 13 g ethanol). Based on the consumption distribution in identified studies, 4 ethanol consumption groups were defined: 1-499, 500-999, 1,000-1,999, and ≥2,000 g/month.
Control	Non-drinkers (cohort or case-control studies) General population rates (studies of alcoholics or brewery workers)
Outcomes	RR (95% CI) of incidence of lung cancer, adjusted and unadjusted for smoking.
Statistical considerations	Random effects model was used for each meta-analysis. No attempt was made to weight studies by quality criteria. Publication bias was evaluated using the adjusted rank correlation funnel plots and test statistic, and the regression asymmetry test. Simulations of cohort studies with various levels of tobacco and alcohol misclassification were conducted to evaluate the possible effects of misclassification on the pooled results from cohort studies.
Results	*Unadjusted for smoking*: Cohort studies, drinker vs non-drinker: 1-499 g/month RR 1.08 (95% CI 0.77, 1.52), 500-599 g/month RR 0.93 (95% CI 0.81, 1.07), 1,000-1,999 g/month RR 1.14 (95% CI 0.89, 1.46), ≥2,000 g/month 2.10 (95% CI 1.45, 3.05), overall (highest alcohol consumption group from each study) RR 1.42 (95% CI 1.16, 1.73) Case-control studies, drinker vs non-drinker: 1-499 g/month RR 1.07 (95% CI 0.63, 1.80), 500-599 g/month RR 1.96 (95% CI 1.48, 2.62), 1,000-1,999 g/month RR 2.52 (95% CI 2.01, 3.15), ≥2,000 g/month 3.57 (95% CI 2.62, 4.88), overall (highest alcohol consumption group from each study) RR 2.18 (95% CI 1.68, 2.84) Studies of alcoholics: RR 1.99 (95% CI 1.66, 2.39) Studies of brewery workers (RR 1.17 (95% CI 0.99, 1.39) *Adjusted for smoking*: Cohort studies, drinker vs non-drinker: 1-499 g/month RR 0.98 (95% CI 0.79, 1.21), 500-599 g/month RR 0.92 (95% CI 0.81, 1.04), 1,000-1,999 g/month RR 1.04 (95% CI 0.88, 1.22), ≥2,000 g/month 1.53 (95% CI 1.04, 2.25), overall (highest alcohol consumption group from each study) RR 1.19 (95% CI 1.11, 1.29) Case-control studies, drinker vs non-drinker: 1-499 g/month RR 0.63 (95% CI 0.51, 0.78), 500-599 g/month RR 1.30 (95% CI 0.98, 1.70), 1,000-1,999 g/month RR 1.13 (95% CI 0.46, 2.75), ≥2,000 g/month 1.86 (95% CI 1.39, 2.49), overall (highest alcohol consumption group from each study) RR 1.39 (95% CI 1.06, 1.83) *Non-smokers*: Evidence from 4 case-control studies and the 2 additional cohort studies from the American Cancer Society was inconsistent and provides no strong evidence for an association between alcohol drinking and lung cancer.
Author's conclusions	At consumption levels below 5 drinks per day, the weight of the evidence suggests that alcohol drinking does not increase the risk of lung cancer and that confounding by cigarette smoking is responsible for any observed associations. For cohort studies, a smoking-adjusted excess of lung cancer was observed only in the highest alcohol consumption category (approximately 5 or more drinks per day) relative to non-drinkers. However, this should be interpreted with caution because the highest alcohol consumption category may be the most vulnerable to residual confounding and was reported in a limited number of studies. Results from population-based case-control studies did not show any association, although a dose-response relation was observed in hospital-based case-control studies.
Reviewer's conclusions/ comments	The highest consumption category was informed by only one cohort and one case-control study. Therefore, a perceived association between ≥2,000 g ethanol/month and lung cancer should be interpreted with caution. The authors assumed one standard drink = 13 g alcohol. Note that in Australia one standard drink is considered equivalent to 10 g alcohol. Study quality was not taken into account. No risk factors other than smoking were considered.
Quality assessment	A. A specific clinical question was not defined; however, the purpose was to review quantitatively the epidemiologic literature on the relation between alcohol consumption and lung cancer risk, with investigation of the role that residual confounding by cigarette smoking may play in producing the observed associations. B. Yes, but suboptimal. The literature search included a search of MEDLINE and manual searching, including reference lists, review articles, and other relevant scientific publications. The date of the search was not reported. C. Unclear. Studies were included if they provided an adequate estimate of RR and a measure of

	precision, or sufficient information for this to be calculated. It is not stated whether eligibility was applied by more than one reviewer. D. No. No attempt was made to assess study quality. E. Yes. The study design and results from individual studies were tabulated. F. Only limited details of the statistical analyses were provided. A pooled RR and 95% CIs associated with alcohol intake was reported. Meta-analyses were conducted using the random effects model. G. No. The authors made no assessment of heterogeneity. However, data from cohort and case-control studies were analysed separately. Furthermore, because of potential differences between hospital-based and population-based case-control studies, an analysis of smoking-adjusted risks was conducted separately for these study types.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

Author (year)	Bagnardi 2001a
Number & type of included studies	Oral cavity & pharynx: 26 studies (1 cohort and 25 cases-control), 7954 cases Oesophagus: 28 studies (1 cohort and 27 case-control), 7239 cases; includes 18 studies of males (1 cohort and 17 case-control, 3310 cases) and 5 studies of females (all case-control, 304 cases) Larynx: 20 studies (all case-control), 3759 cases Breast: 49 studies (12 cohort and 37 case-control), 44033 cases Colon & rectum: 22 studies (6 cohort and 16 case-control), 11296 cases Liver: 20 studies (3 cohort and 17 case-control), 2294 cases; includes 10 studies of males (2 cohort and 8 case-control, 949 cases) and 3 studies of females (1 cohort and 2 case-control, 231 cases) Pancreas: 17 studies (4 cohort and 13 case-control), 2524 cases Lung: 6 studies (3 cohort and 3 case-control), 2314 cases Prostate: 11 studies (4 cohort and 7 case-control), 4094 cases Ovary: 5 studies (all case-control), 1651 cases Stomach: 16 studies (2 cohort and 14 case-control), 4518 cases Small intestine: 2 studies (both case-control), 415 cases Gallbladder: 2 studies (1 cohort and 1 case-control), 81 cases Melanoma: 2 studies (both case-control), 708 cases Cervix: 1 study (case-control), 242 cases Endometrium: 6 studies (2 cohort and 4 case-control) Kidney: 2 studies (both case-control), 921 cases All sites together: 8 studies (6 cohort and 2 case-control), 14495 cases
List of included studies	Details of included studies not provided.
Population	Not specifically defined. Results shown separately for males and females for the risk of oesophageal cancer because there was a statistically significant gender difference in modifying the effect of alcohol intake.
Exposure	Only those studies that considered at least 3 levels of alcohol consumption and reported the number of cases and non-cases, and the estimates of the odds ratios or RR for each exposure level were eligible for inclusion. The 3 exposure levels were as follows : 25 g/day (ie, approximately 2 drinks), 50 g/day (ie, approximately 4 drinks), 100 g/day (ie, approximately 8 drinks)
Control	Not stated but assume relative to non-alcohol drinkers (as per similar publication from the same authors - Corrao *et al*, 2004). The authors state that a limitation of the study is the absence of distinction between lifelong abstainers and former drinkers in several of the individual studies.
Outcomes	RR (95% CI) of incidence of particular cancers for selected doses of alcohol intake
Statistical considerations	Data from individual studies were pooled and the relationship between alcohol consumption and risk was modelled by fitting several fractional models in order to identify J- or U-shaped curves, or other relationships. A family of second-order models was generated by power transformation of the exposure variable, and the best-fitting model was chosen to summarise the relation of interest. Pooled estimates of adjusted and unadjusted RRs were compared to investigate the effects of gender and smoking. Heterogeneity was evaluated using the method of Greenland & Longnecker (1992).
Results	Oral cavity & pharynx: 25 g/day RR 1.75 (95% CI 1.70, 1.82); 50 g/day RR 2.85 (95% CI 2.70, 3.04); 100 g/day RR 6.01 (95% CI 5.46, 6.62); no significant gender effect; heterogeneity $P<0.05$. Oesophagus: 25 g/day RR 1.51 (95% CI 1.48, 1.55); 50 g/day RR 2.21 (95% CI 2.11, 2.31); 100 g/day RR 4.23 (95% CI 3.91, 4.59); gender effect $P<0.05$; heterogeneity $P<0.05$. Males: 25 g/day RR 1.43 (95% CI 1.38, 1.48); 50 g/day RR 1.98 (95% CI 1.87, 2.11); 100 g/day RR 3.49 (95% CI 3.14, 3.89); heterogeneity $P<0.05$. Females: 25 g/day RR 1.52 (95% CI 1.42, 1.63); 50 g/day RR 2.24 (95% CI 1.95, 2.58); 100 g/day RR 4.45 (95% CI 3.37, 5.87). Larynx: 25 g/day RR 1.38 (95% CI 1.32, 1.45); 50 g/day RR 1.94 (95% CI 1.78, 2.11); 100 g/day RR 3.95 (95% CI 3.43, 4.57); no significant gender effect; heterogeneity $P<0.05$. Breast: 25 g/day RR 1.31 (95% CI 1.27, 1.36); 50 g/day RR 1.67 (95% CI 1.56, 1.78); 100 g/day RR 2.71 (95% CI 2.33, 3.08); no significant gender effect; heterogeneity $P<0.05$. Colon & rectum: 25 g/day RR 1.08 (95% CI 1.06, 1.10); 50 g/day RR 1.18 (95% CI 1.14, 1.22); 100 g/day RR 1.38 (95% CI 1.29, 1.49); no significant gender effect; heterogeneity $P<0.05$. Liver: 25 g/day RR 1.17 (95% CI 1.11, 1.23); 50 g/day RR 1.36 (95% CI 1.23, 1.51); 100 g/day RR 1.86 (95% CI 1.53, 2.27); gender effect $P<0.05$; heterogeneity $P<0.05$. Males: 25 g/day RR 1.28 (95% CI 1.13, 1.45); 50 g/day RR 1.51 (95% CI 1.27, 2.10); 100 g/day RR

	1.62 (95% CI 1.18, 2.24); heterogeneity $P<0.05$. Females: 25 g/day RR 1.97(95% CI 1.30, 3.00); 50 g/day RR 3.57 (95% CI 1.56, 8.21); 100 g/day RR 9.15 (95% CI 1.73, 48.41). Pancreas: 25 g/day RR 0.98 (95% CI 0.90, 1.05); 50 g/day RR 1.05 (95% CI 0.93, 1.18); 100 g/day RR 1.18 (95% CI 0.94, 1.49); no significant gender effect; heterogeneity $P<0.05$. Lung: 25 g/day RR 1.02 (95% CI 1.00, 1.04); 50 g/day RR 1.04 (95% CI 1.00, 1.08); 100 g/day RR 1.08 (95% CI 1.00, 1.18); no significant gender effect; heterogeneity $P<0.05$. Prostate: 25 g/day RR 1.05 (95% CI 1.00, 1.08); 50 g/day RR 1.09 (95% CI 1.02, 1.17); 100 g/day RR 1.19 (95% CI 1.03, 1.37); no heterogeneity. Ovary: 25 g/day RR 1.11 (95% CI 1.00, 1.24); 50 g/day RR 1.23 (95% CI 1.01, 1.54); 100 g/day RR 1.53 (95% CI 1.03, 2.32); no heterogeneity. Stomach: 25 g/day RR 1.07 (95% CI 1.04, 1.10); 50 g/day RR 1.15 (95% CI 1.09, 1.22); 100 g/day RR 1.32 (95% CI 1.18, 1.49); no significant gender effect; heterogeneity $P<0.05$. Small intestine: 25 g/day RR 1.02 (95% CI 0.89, 1.17); 50 g/day RR 1.04 (95% CI 0.79, 1.37); 100 g/day RR 1.08 (95% CI 0.63, 1.88); no significant gender effect; no heterogeneity. Gallbladder: 25 g/day RR 1.17 (95% CI 0.73, 1.86); 50 g/day RR 1.36 (95% CI 0.54, 3.44); 100 g/day [no studies reported effect at this dose]; no significant gender effect; no heterogeneity. Melanoma: 25 g/day RR 0.50 (95% CI 0.21, 1.10); 50 g/day [no studies reported effect at this dose]; 100 g/day [no studies reported effect at this dose]; no significant gender effect; no heterogeneity. Cervix: 25 g/day RR 0.80 (95% CI 0.50, 1.27); 50 g/day RR 0.64 (95% CI 0.25, 1.60); 100 g/day [no studies reported effect at this dose]; no heterogeneity. Endometrium: 25 g/day RR 1.05 (95% CI 0.88, 1.24); 50 g/day RR 1.09 (95% CI 0.78, 1.54); 100 g/day RR 1.20 (95% CI 0.60, 2.37); heterogeneity $P<0.01$. Kidney: 25 g/day RR 0.88 (95% CI 0.77, 1.02); 50 g/day RR 0.79 (95% CI 0.60, 1.03); 100 g/day RR 0.62 (95% CI 0.36, 1.06); no significant gender effect; no heterogeneity. Bladder: 25 g/day RR 1.04 (95% CI 0.99, 1.09); 50 g/day RR 1.08 (95% CI 0.98, 1.19); 100 g/day RR 1.17 (95% CI 0.97, 1.41); no significant gender effect; no heterogeneity. All sites together: 25 g/day RR 1.01 (95% CI 0.90, 1.05); 50 g/day RR 1.22 (95% CI 1.11, 1.27); 100 g/day RR 1.91 (95% CI 1.77, 2.06); no significant gender effect; heterogeneity $P<0.05$.
Author's conclusions	Strong trends in risk were observed for cancers of the oral cavity and pharynx, oesophagus and larynx. Less strong direct relationships were observed for cancers of the stomach, colon & rectum, liver, breast, and ovary. No significant nor consistent relationship was observed for cancers of the pancreas, lung, prostate, or bladder. Gender explained a significant part of the observed heterogeneity for cancer of the oesophagus and liver, with higher risks in women. Allowance for tobacco appreciably modified the relationship between alcohol and the risk of laryngeal, lung, and bladder cancers, but not oral or oesophageal cancers. The meta-analysis showed no evidence of a threshold effect for most alcohol-related neoplasms.
Reviewer's conclusions/ comments	No assessment was made of the quality of the included studies. It is not clear how many of the individual studies adjusted estimates for the main risk covariates. It is unclear why the authors refer to a moderate excess risk of bladder cancer in the discussion when the trend is non-significant. No citations or details of the individual studies were provided in the publication and therefore it is not known if any of the included studies were Australian.
Quality assessment	A. A specific clinical question was not defined; however, the major focus was stated: to evaluate the effect of alcohol on cancer risk. B. Yes. Included electronic and manual searching to 2000, including a hand-search on the most relevant journals of epidemiology and medicine, and a manual search of published general reviews and meta-analyses on the issue. C. Yes. Studies were included if they were a case-control or cohort study published as an original article, expressed findings as OR or RR, considered at least 3 levels of alcohol consumption, reported the number of cases and non-cases, and estimated the OR or RR for each exposure level. The eligibility of each paper was independently determined by two assessors who were blinded to the author's names and affiliations and the results pertaining to alcohol consumption. D. No. The author's made no assessment of the quality of the included studies. E. No. The study details and results of individual studies were not presented. The publication showed aggregated and meta-analysed data only. F. Yes. The authors refer to earlier papers for details of the statistical methods used for meta-analysis. According to the earlier publications, random effects models were used when there was evidence of significant heterogeneity. A pooled RR and 95% CIs associated with alcohol intake was reported for each type of neoplasm, based on multivariate estimates directly obtained from the β coefficients of the best fitting model. G. Yes. Heterogeneity among studies was evaluated according to the method described by

	Greenland & Longnecker (1992). Gender was included in the meta-regression models to control for heterogeneity due to gender differences in alcohol metabolism. The effects of smoking adjustment in modifying alcohol related risks were investigated by comparing pooled estimates that were adjusted and unadjusted for tobacco.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

Author (year)	**Ridolfo & Stevenson 2001** **Chapter in The quantification of drug-caused mortality and morbidity in Australia, 1998**
Number & type of included studies	16 new studies included, then added to the original 29 studies of English 1995. Studies that reported relative risks relative to abstinence (rather than low alcohol). 9 case-control 7 cohort
List of included studies	16 included studies after removal of duplicates; Ferraroni 1998 Bowlin 1997 Royo Bordonada 1997 Swanson 1997 Thun 1997 Haile 1996 Boice 1995 Freudenheim 1995 Holmberg 1995 Longnecker 1995a Longnecker 1995b van den Brandt 1995 Katsouyanni 1994 Nasca 1994 Begg 1983 Byers & Funch 1982 These were then combined with the 29 studies included in the original English (1995) review: Chu 1989 Ewertz 1991 Ferraroni 1991 Franceschi 1991 Harvey 1987 Hiatt & Bawol 1984 Hiatt 1988 La Vecchia 1989 La Vecchia 1985 Le 1984 Nasca 1990 O'Connell 1987 Rosenburg 1990 Schatzkin 1987 Simon 1991 Toniolo 1989 Webster 1983 Adami 1988 Friedenreich 1993 Harris 1992 Martin Moreno 1993 Meara 1989 Richardson 1989 Rohan & McMichael 1988 Sneyd 1991 Willett 1987 van't Veer 1989 Gapstur 1992 Garfinkel 1988
Population	Breast cancer cases (applied to Australian female population)
Outcomes	Breast cancer risk
Author's conclusions	Risk was significantly elevated for all levels of alcohol consumption relative to abstinence

	Risk ratios: Low 1.14 (1.09, 1.20) Medium 1.41 (1.32, 1.50) High 1.59 (1.43, 1.78) No difference in RR between women under and over 45 years, therefore combined estimates reported.
Reviewer's comment	Update of English 1995, but results expressed relative to abstinence rather than low-alcohol consumption. English and colleagues calculated the RR and aetiological fractions relative to low consumption to reflect the concept that unsafe drinking, as opposed to low alcohol consumption which may be protective, is the cause for concern. Ridolfo and colleagues departed from this approach and derived fractions relative to non-drinkers. A total of 16 additional studies identified in the update were added to the 29 studies originally included in the meta-analysis conducted by English et al. The authors then applied risk estimates to Australian alcohol consumption estimates from ABS National Health Survey to estimate aetiological fractions for alcohol exposure and breast cancer.

Abbreviations: ABS, Australian Bureau of Statistics; CI, confidence interval; RR, relative risk

Author (year)	Dennis 2000
Number & type of included studies	7 cohort studies - 6 studies were used in the meta-analysis. 28 case-control studies (15 with population-based controls, 11 with hospital controls, and 2 with benign prostatic hyperplasia as controls) – 27 studies were used in the meta-analysis.
List of included studies	*Cohort studies*: Cerhan (1997) Hiatt (1994) Le Marchand (1994) Hirayama (1992) Hsing (1990) Stemmerman (1990) Mills (1989) *Case control*: Andersson (1996) Gronberg (1996) Hayes (1996) Pawlega (1996) Hsing (1994) Nakata (1993) Slattery & West (1993) Walker (1992) Fincham (1990) Hinda (1988) Ross (1987) Whittemore (1985) Chaklin & Plotnikov (1984) Mishina (1981) Schuman (1977) Lumey (1997) Ewings & Bowie (1996) De Stefani (1995) Tavani (1994) Wei (1994) Mettlin (1989) Yu (1988) Talamini (1986) Jackson (1981) Niijima (1980) Wynder (1971) Van der Gulden (1991) Checkoway (1987)
Population	Not specifically defined.
Exposure	'Ever' drinking, for comparison of 'ever' vs 'never' drinking. For the dose-response analysis, consumption categories 1 drink/day, 2 drinks/day, 3 drinks/day, 4 drinks/day. Also examined ≥1 drink/day vs <1 drink/day.
Control	'Never' drinking. Additional analysis with <1 drink/day as control vs ≥1 drink/day
Outcomes	RR of prostate cancer incidence, for all studies and by study design and method of data abstraction.
Statistical considerations	If a RR estimate for 'never' vs 'ever' drinking was not reported, then the reported RR for all levels of alcohol consumption vs 'never' drinking were pooled using the inverse variance method. Otherwise, the RR was estimated by reported data. If studies stated that they found no association but did not report a RR, then those studies were assigned a RR estimate of 1.0. An overall pooled RR was calculated based on a fixed effects model, using the inverse variance method. The random effects model was used as a supportive analysis. Heterogeneity was assessed using the Chi-square score. A potential dose-response relationship was examined using the technique of Berlin *et al* (1993),

	along with covariance-adjusted risks according to Greenland & Longnecker (1992), with no adjustment for covariates. A linear dose-response was assumed. Data were adjusted for the covariances of individual studies.
Results	*'Ever' vs 'never' analysis*: All studies (n=33): RR 1.05 (95% CI 0.98, 1.11) Cohort studies (n=6): RR 1.00 (0.89, 1.13) Case control studies (n=27): RR 1.05 (95% CI 0.98, 1.13) Based on method of data abstraction, RR varied from 0.98 (95% CI 0.80, 120) to 1.08 (95% CI 0.93, 1.24). Highest risk in beer drinkers. No heterogeneity based on Chi-square *P*-value. *Dose response (all studies n=15)*: 1 additional drink/day RR 1.05 (95% CI 0.91, 1.20) 2 additional drinks/day RR 1.10 (95% CI 0.96, 1.26) 3 additional drinks/day RR 1.15 (95% CI 1.00, 1.32) 4 additional drinks/day RR 1.21 (95% CI 1.05, 1.39)
Author's conclusions	The meta-analysis suggests that there is no relationship between moderate alcohol consumption and prostate cancer. While the highest categories of consumption showed an increased risk, the studies reporting such categories appeared to be biased towards reporting a positive association among the categories.
Reviewer's conclusions/ comments	Case-control studies not included. 6 of the 33 included studies reported risks adjusted for smoking.
Quality assessment	A. A specific clinical question was not defined; however, the purpose of the study was to apply a detailed meta-analytic approach for combining RR estimates from studies on the relationship between prostate cancer incidence and alcohol consumption to estimate the effect size of the RR estimate. B. Yes. Included electronic and manual searching between 1976 and July 1998, including seeking "leads from colleagues" and examining articles on risk factors for prostate cancer to identify unpublished RR estimates for prostate cancer and alcohol consumption. C. Yes. Studies were eligible for inclusion if they examined alcohol consumption prior to the development of prostate cancer. Studies reporting less than one drink/day as the reference rather than never consumption were excluded. D. No. The authors made no attempt to assess study quality. E. Yes. The study details and results of individual studies were appropriately summarised. F. Yes. In addition to pooling all identified studies, separate analyses were conducted based on study design and method of data abstraction. Data were analysed using the fixed effects model and the random effects model. A pooled RR and 95% CIs associated with alcohol intake was reported. G. Yes. Heterogeneity in results across studies was examined using Chi-square score for each of the analyses conducted. The studies were generally homogeneous. One cohort study which reported fatal prostate cancer among daily drinkers was found to be an outlier.

The quality of systematic reviews was assessed using the following questions: (A) Was a clinical question clearly defined?; (B) Was an adequate search strategy used?; (C) Were the inclusion criteria appropriate and applied in an unbiased way?; (D) Was a quality assessment of included studies undertaken?; (E) Were the characteristics and results of the individual studies appropriately summarised?; (F) Were the methods for pooling the data appropriate?; (G) Were sources of heterogeneity explored?

NON-SELECTED SYSTEMATIC REVIEWS

Author (year)	Donato (2006)
Number & type of included studies	Case-control or cohort studies. Referred to 11 studies that investigated alcohol and risk of HCC.
List of included studies	*Referring to alcohol and risk of cancer:* Corrao (1993, 1997) Bellentani (1994) Corrao & Arico (1998) Kuper (2000) Klatsky & Armstrong (1992) Becker (2002) Sorensen (1998) Kamper-Jorgensen (2004) Donato (2002) Covolo (2005) Yuan (2004)
Population	Cases of HCC
Outcomes	OR with heavy alcohol intake ± HBV or HCV infection
Author's conclusions	The pattern of risk for HCC because of alcohol intake shows a continuous dose-effect curve without a definite threshold, although most studies found that HCC risk increased only for alcohol consumption above 40-60 g of ethanol per day. Most studies with accurate control for confounding show a significant increase in HCC risk at 40 g ethanol per day (possibly 20 g per day in women). Some evidence supports a positive interaction of alcohol intake probably with HCV infection and possibly with HBV infection.
Reviewer's comment	Selected studies in Southern Europe. Descriptive reporting of findings. A meta-analysis was not conducted.

Abbreviations: HCC, hepatocellular carcinoma; OR, odds ratio; HBV, hepatitis B virus; HCV, hepatitis C virus

Author (year)	Herbey (2005)
Number & type of included studies	66 studies investigating risk factors causing colorectal cancer and hypercholesterolemia. Only 2 studies refer to alcohol, one of which was an animal study.
List of included studies	*Referring to alcohol and risk of cancer:* Pederson (2003) Roy (2002) – animal study
Population	Cases of colorectal cancer or hypercholesterolemia, human or animal
Outcomes	Risk factors for colorectal cancer and hypercholesterolemia
Author's conclusions	No conclusions of relevance.
Reviewer's comment	Literature search 1990-2005. Reviews risk factors leading to the development of colorectal cancer and hypercholesterolemia. Descriptive reporting of findings. Relative risks not reported. A meta-analysis was not conducted.

Author (year)	Althuis et al (2004)
Number & type of included studies	31 publications (1 RCT, 10 cohort, 20 case-control) representing 24 distinct study populations
List of included studies	Colditz 2004 Chlebowski 2003 Palmer 2002 Sellers 2002 Sellers 2002 Potter 1995 Tutera 1996 (reported as 1995 in Table 1)

	Gapstur 1995 London 1989 Manjer 2001 Wohlfahrt 1999 McCredie 2003 Cotterchio 2003 Li 2003 Baumgartner 2002 Zhu 2002 Althuis 2003 Britton 2002 Enger 2000 Enger 1999 Huang 2000 Morabia 1998 Nasca 1994 Kreiger 1991 Cooper 1989 Hislop 1986 Stanford 1987 McTiernan 1986 Yoo 2001 Yoo 1997 Hildreth 1983
Population	Breast cancer patients classified by hormone-receptor status
Outcomes	Breast cancer risk. Mortality not investigated.
Author's conclusions	Risks associated with alcohol consumption did not differ by receptor status. Online appendix provides alcohol risk estimates reported by individual studies, by hormone status (NB. Results not meta-analysed, but appeared independent of receptor-status).
Reviewer's comment	Alcohol use not a major focus of the review. Focus was upon underlying differences in risk profile between breast cancers when classified by their receptor status.

Author (year)	**Burger (2004)**
Number & type of included studies	> 350 studies evaluated to develop evidence base for risk-benefit analysis of moderate alcohol consumption (≤ 40 g alcohol/day) and various health outcomes. Cancer of the mouth, pharynx, larynx, & oesophagus: 3 prospective and 38 case-control studies Cancer of the breast: 14 prospective and 27 case-control studies Cancer of the colon & rectum: 4 prospective and 10 case-control studies
List of included studies	*Cancer-related papers:* GronBaek (1998) Kjaerheim (1998) Kato (1992) Maier (1999) De Stefani (1998) Schildt (1998) Talamini (1998) Dosemeci (1997) Morse (1996) Bundgaard (1995) Brown (1994) Franceschi (1994) Hedberg (1994) Maier (1994) Tavani (1994) Kabat (1993) Mashberg (1993)

	Ng (1993) Tavani (1993) Franceschi (1992) Muscat (1992) Negri (1992) Ahrens (1991) Oreggia (1991) Sankaranarayanan (1991) Winn (1991) Zatonski (1991) Barra (1990) De Stefani (1990) Franceschi (1990) Talamini (1990) Falk (1989) Franco (1989) Kabat (1989, 1989) La Vecchia (1989) Merletti (1989) Blot (1988) Brown (1988) Tuyns (1988) Yu (1988) Thun (1997) Fuchs (1995) Zhang (1999) Gapstur (1995) Van den Brandt (1995) Friedenreich (1993) Adami (1992) Gapstur (1992) Simon (1991) Garfinkel (1988) Hiatt (1988) Reynolds (1988) Schatzkin (1987, 1989) Willett (1987) Enger (1999) Franceschi (1998) Mezzetti (1998) Bowlin (1997) Decarli (1997) Royo-Bordonada (1997) Swanson (1997) Viel (1997) Levi (1996) Viladiu (1996) Weiss (1996) Freudenheim (1995) Holmberg (1995) Longnecker (1995, 1995) Ranstam (1995) Katsouyanni (1994) Nasca (1994) Smith (1994) Herrinton (1993) Martin-Moreno (1993)

	Ewertz (1991) Ferraroni (1991) Franceschi (1991) Sneyd (1991) Nasca (1990) Rosenberg (1990) Smith-Warner (1998) Longnecker (1994) Roth (1994) Howe (1991) Hsing (1998) Giovannucci (1995) Gapstur (1994) Goldbohm (1994) Tavani (1998) Gerhardsson (1993) Meyer (1993) Newcomb (1993) Barra (1992) Benito (1991) Riboli (1991) Longnecker (1990) Slattery (1990) Peters (1989)
Population	Studies on participants of African or Asian origin excluded.
Outcomes	Description of general findings from included studies regarding moderate alcohol consumption and the risk of cancer.
Author's conclusions	The tolerable upper alcohol intake levels for the German population were set at 10-12 g/day for healthy women and 20-24 g/day for healthy men.
Reviewer's comment	Literature search 1988-1999. Quality assessment of included studies undertaken and more weight was given to those with a higher score if results were conflicting. RR not reported and meta-analysis not conducted.

Author (year)	**Shi & Copas, 2004**
Number & type of included studies	13 of 16 studies from original Longnecker 1988 paper.
List of included studies	Hiatt & Bawol, 1984 Hiatt 1988 Willett 1987 Schatzkin 1987 Harvey 1987 Rosenberg 1982 Webster 1983 Paganani-Hill & Ross 1983 Byers & Funch 1982 Rohan & McMichael 1988 Le 1984 La Vecchia 1985 Begg 1983
Population	Breast cancer cases
Outcomes	Breast cancer risk. Mortality not investigated.
Author's conclusions	A meta-analysis of epidemiological studies on the effect of alcohol on the risk of breast cancer is used to illustrate a statistical model that allows for arbitrarily aggregated dose levels. The results suggest that the rate of increase in risk with alcohol consumption is substantially less than has been previously suggested.

Reviewer's comment	Re-analysis of Longnecker 1988 and Greenland 1992 Predominantly methodological paper. Attempts to overcome deficiencies in methods, to allow for studies that report different exposure levels for alcohol, heterogeneity and publication bias. The paper confirms that the risk result is indeed dependent upon what assumptions are made in relation to these issues.

Author (year)	**Zeegers (2004)**
Number & type of included studies	Epidemiologic studies (follow-up studies, case-control studies, controlled trials) investigating the effects of smoking, beverage consumption, and diet on risk of bladder cancer. Referred to their earlier paper describing a meta-analysis of 30 epidemiologic studies. Note that this study focused on tea and coffee consumption, not alcohol. Unclear why authors referred to it.
List of included studies	Zeegers 2001
Population	Cases of bladder cancer
Outcomes	RR of bladder cancer, adjusted for smoking
Author's conclusions	Previous study showed a small, non-significant increased cigarette-smoking adjusted risk of bladder cancer from alcohol consumption for men (RR 1.3, 95% CI 0.9-2)
Reviewer's comment	Refers to previous study from the same authors without identification of any other studies. The previous study does not report alcohol consumption at all. Unclear where the data came from. Descriptive reporting of findings only.

Author (year)	**Mack (2003)**
Number & type of included studies	14 case-control studies of risk factors and risk of thyroid cancer. 10 studies collected data on beer and wine consumption
List of included studies	*Referring to alcohol and risk of cancer:* Ron (1987) Preston-Martin (1987) Kolonel (1990) Preston-Martin (1993) Levi (1993) D'Avanzo (1995) Linos (1989) Galanti (1997) Glattre (1993)
Population	Cases of thyroid cancer
Outcomes	OR of thyroid cancer with any alcohol intake.
Author's conclusions	Weekly drinks of wine and beer $P = 0.02$. After adjustment for current smoking $P = 0.12$. > 14 drinks/week OR 0.8 (95% CI 0.6-1.0), after smoking adjustment OR 0.9 (95% CI 0.7-1.1). No increased risk with higher levels of alcohol consumption. If anything, there may be a decreased risk with greater consumption. However, this data is confounded by smoking since adjustment for current smoking eliminated any alcohol-related trends in thyroid cancer risk.
Reviewer's comment	No standard units or quantifiable alcohol content. Based on beer and wine consumption only.

Abbreviations: CI, confidence interval; OR, odds ratio

Author (year)	**Okasha 2003**
Number & type of included studies	7 case-control studies
List of included studies	Ferraroni 1998 Kinney 2000 Marcus 2000 Nasca 1990

	Smith 1994 Swanson 1997 Van-t Veer 1989
Population	Breast cancer cases classified by pre-adult exposures (height, weight, smoking, diet, physical activity, alcohol consumption)
Outcomes	Breast cancer risk. Mortality not investigated.
Author's conclusions	No clear association between early drinking and breast cancer risk. Authors state results are at odds with those of Colditz & Frazier 1995, who suggested that the risk of breast cancer could be reduced if the age of commencement of drinking was delayed
Reviewer's comment	Alcohol use not a major focus of the review. Investigates impact of various pre-adult exposures

Author (year)	**Bagnardi (2001b)**
Number & type of included studies	229 studies (183 case-control and 46 cohort) which reported a total of 115, 199 cases
List of included studies	Not provided.
Population	Cancer cases at 19 sites in the body or at all sites combined.
Outcomes	Pooled estimate of RR (95% CI) of incidence of cancer, associated with alcohol intake of 25 g/day, 50 g/day, and 100 g/day.
Author's conclusions	Alcohol most strongly increased the risks for cancers of the oral cavity, pharynx, oesophagus, and larynx. Statistically significant increases in risk also existed for cancers of the stomach, colon, rectum, liver, female breast, and ovaries. Concurrent tobacco use enhances alcohol's effects on the risk for cancers of the upper digestive and respiratory tract. The analysis was unable to identify a threshold level of alcohol consumption below which no increased risk of cancer is evident.
Reviewer's comment	RRs similar but not identical to those reported in Bagnardi (2001a). Includes 1 less liver study than Bagnardi 2001a and separates out cancer of the colon and rectum.

Abbreviations: CI, confidence interval; RR, relative risk

Author (year)	**Ellison 2001**
Number & type of included studies	40 studies (incidence) 2 studies (mortality)
List of included studies	Adami 1988 Bowlin 1997 Chu 1989 Ewertz 1991 Ferraroni 1991 Ferraroni 1998 Freudenheim 1995 Friedenreich 1993 Fuchs 1995 Gapstur 1992 Garfinkel 1988 Graham 1992 Harris 1992 Harvey 1987 Hiatt & Bawol 1984 Hiatt 1988 Holmberg 1995 Howe 1991 Hoyer & Engholm 1992 Katsouyanni 1994 La Vecchia 1989 Levi 1996

	Longnecker 1995 Longnecker 1995 Martin-Moreno 1993 Meara 1989 Mezzetti 1998 Nasca 1990 Ranstam 1995 Richardson 1989 Rosenberg 1990 Royo-Bordonada 1997 Schatzkin 1987 Simon 1991 Smith 1994 Sneyd 1991 Swanson 1997 Van den Brandt 1995 Van 't Veer 1989 Viladiu 1996 Willett 1987 Willett 1998 Young 1989 Zhang 1999 Smith-Warner 1998
Population	Breast cancer cases
Outcomes	Breast cancer risk (2 studies on breast cancer mortality also reported, but not meta-analysed)
Author's conclusions	Overall there was a monotonic increase in relative risk of breast cancer with alcohol consumption, but the magnitude was small. RR 1.10 (1.06, 1.14) for 12 g/day relative to non-drinkers
Reviewer's comment	Result potentially influenced by higher relative risks in the hospital-based case-control studies, and those with shorter follow-up. When limited to 5 most recent US cohort studies, effect was of borderline statistical significance.

Abbreviations: CI, confidence interval; RR, relative risk

Author (year)	**Gutjahr (2001)**
Number & type of included studies	Review and original papers dealing with alcohol-related health effects Three major social-cost and mortality studies were included. Number of studies identified from the literature search not stated.
List of included studies	Three major social-cost and mortality studies & 2 additional papers "with a different scope": English (1995) Single (1996) Shultz (1991) Dufour & Caces (1993) Fox (1995) Other studies referred to in the text.
Population	Fatal medical conditions attributed to alcohol
Outcomes	Descriptive reporting of findings from studies that examined the relationship between alcohol and fatal medical conditions.
Author's conclusions	The authors do not agree with the contention of Single *et al* (1996) that studies "generally include the same causes of morbidity and mortality". Rather, the authors found considerable divergence. The authors stated that "the present review reveals that the investigation of English *et al* (1995) is still up to date. The number of diagnoses not included by English *et al* but sustained by sufficient scientific evidence is restricted to fewer than a dozen, which include lip cancer, various carcinomas, diabetes, and several external causes (eg, accidents).
Reviewer's comment	Updates the study by English *et al* (1995). RRs not reported and a meta-analysis was not conducted. Compared 3 major social-cost studies with respect to alcohol-related causes of mortality. A systematic literature search was conducted only on discordant and less-known conditions.

Author (year)	Dhote (2000)
Number & type of included studies	44 studies (8 cohort & 36 case-control studies) of risk factors for RCC. 6 case-control studies assessed the relationship between alcohol consumption and RCC.
List of included studies	*Referring to alcohol and risk of cancer:* Mellemgaard (1994, 1994) Muscat (1995) Wolk (1996) Lindblad (1997)
Population	Cases of RCC
Outcomes	OR of RCC with alcohol consumption
Author's conclusions	No association between alcohol intake and RCC was observed in men. A protective effect of alcohol 2-10 drinks per week was seen in women.
Reviewer's comment	Not specifically a report of effect of alcohol on cancer risk. Descriptive reporting of findings. A meta-analysis was not conducted.

Abbreviations: OR, odds ratio; RCC, renal cell carcinoma

Author (year)	Corrao (1999)
Number & type of included studies	200 case-control and cohort studies (including 97, 351 cases) reporting estimates of RR of incidence of condition for ≥ 3 doses of alcohol. Included studies of several conditions commonly considered (or suspected) to be causally and positively associated with alcohol intake: cancers of the lip, oral cavity & pharynx, oesophagus, colon & rectum, liver, larynx, and breast.; cases of essential hypertension, cerebrovascular diseases, gastric & duodenal ulcer, cirrhosis & other chronic diseases of the liver, chronic pancreatitis, and injuries and adverse events. Dose-response slopes and RRs based on 123 studies (including 62, 134 cases) with higher quality score and/or reported adjusted estimates of RR.
List of included studies	Not provided. Available from authors on request.
Population	Cases of the specific conditions listed above.
Outcomes	Pooled estimates of RR (95% CI) of incidence of cancer, associated with alcohol intake of 25 g/day, 50 g/day, and 100 g/day, stratified by sources of heterogeneity and alcohol terms which had been significant in previous analyses.
Author's conclusions	Lip, oral cavity & pharynx: *Men/Mediterranean* 25 g/day RR 2.2 (95% CI 1.9, 2.5), 50 g/day RR 4.2 (95% CI 3.0, 5.5), 100 g/day RR 10.7 (95% CI 4.6, 24.9); *Women/Mediterranean* RR 2.3 (95% CI 1.7, 3.0), 50 g/day RR 4.5 (95% CI 2.4, 7.7), 100 g/day RR 12.5 (95% CI 2.8, 55.4); *Men/Other areas* 25 g/day RR 1.9 (95% CI 1.5, 2.3), 50 g/day RR 3.0 (95% CI 1.9, 4.8), 100 g/day RR 5.5 (95% CI 1.7, 17.0); *Women/Other areas* RR 1.9 (95% CI 1.3, 2.8), 50 g/day RR 3.2 (95% CI 1.5, 7.1), 100 g/day RR 6.4 (95% CI 1.1, 37.7) Oesophagus: *Mediterranean* 25 g/day RR 1.6 (95% CI 1.5, 1.7), 50 g/day RR 2.5 (95% CI 2.2, 2.8), 100 g/day RR 6.0 (95% CI 4.6, 7.8); *Other areas* RR 1.5 (95% CI 1.3, 1.7), 50 g/day RR 2.2 (95% CI 1.7, 2.8), 100 g/day RR 4.5 (95% CI 2.6, 7.8) Colon: *Case-control studies* 25 g/day RR 1.0 (95% CI 1.0, 1.1), 50 g/day RR 1.1 (95% CI 1.0, 1.2), 100 g/day RR 1.1 (95% CI 1.0, 1.3); *Cohort studies* RR 1.4 (95% CI 1.1, 1.7), 50 g/day RR 1.9 (95% CI 1.3, 2.9), 100 g/day RR 3.6 (95% CI 1.6, 8.5) Rectum: *Men* 25 g/day RR 1.1 (95% CI 1.0, 1.2), 50 g/day RR 1.2 (95% CI 1.1, 1.5), 100 g/day RR 1.5 (95% CI 1.2, 2.2); *Women* RR 2.3 (95% CI 1.3, 4.0), 50 g/day RR 5.0 (95% CI 1.6, 16.4), 100 g/day RR 25.7 (95% CI 2.5, 267.6) Liver: *All* 25 g/day RR 1.2 (95% CI 1.1, 1.3), 50 g/day RR 1.4 (95% CI 1.2, 1.6), 100 g/day RR 1.8 (95% CI 1.2, 2.6) Larynx: *Mediterranean* 25 g/day RR 1.6 (95% CI 1.6, 1.7), 50 g/day RR 2.7 (95% CI 2.4, 2.9), 100 g/day RR 7.1 (95% CI 5.8, 18.6); *Other areas* RR 1.2 (95% CI 1.1, 1.3), 50 g/day RR 1.5 (95% CI 1.2, 1.8), 100 g/day RR 2.1 (95% CI 1.4, 3.1) Breast: *Mediterranean* 25 g/day RR 1.4 (95% CI 1.3, 1.5), 50 g/day RR 1.8 (95% CI 1.6, 2.1), 100 g/day RR 3.4 (95% CI 2.6, 4.6); *Other areas* RR 1.2 (95% CI 1.0, 1.4), 50 g/day RR 1.5 (95% CI 1.1, 2.0), 100 g/day RR 2.2 (95% CI 1.1, 4.0) The small number of sufficiently reliable studies, the strong indications of heterogeneity across

	them and the suspicion of publication bias suggests that there is a need for well-conducted epidemiological studies performed in several countries, to examine the dose-response relationship between alcohol intake and the risk of several alcohol-related conditions, as well as the role of drinking pattern in determining the risk. For all cancers, there was a clear trend towards increasing RR at increased alcohol intake. Significant risks were found for the lowest doses of alcohol considered (25 g alcohol or 2 drinks per day). However these estimates were based on models that did not fit the data very well.
Reviewer's comment	Literature search 1966 through 1998. *Superseded* by Bagnardi *et al* (2001) and Corrao *et al* (2004)

Abbreviations: CI, confidence interval; RR, relative risk

Author (year)	**Tseng 1999**
Number & type of included studies	N/A, uses result of Longnecker 1994
List of included studies	N/A, uses result of Longnecker 1994
Population	Applied to US population
Outcomes	Breast cancer rates
Author's conclusions	The estimated age-adjusted population attributable risk for alcohol and breast cancer was 2.1%. Therefore, widespread efforts to reduce alcohol consumption would not have a substantial impact on breast cancer rates in this population.
Reviewer's comment	Not original meta-analysis, rather an estimate of population attributable risk based on previously published meta-analysis, SEER statistics and general population data.

Author (year)	**Zeegers (1999)**
Number & type of included studies	16 observational epidemiological studies (3 follow-up studies, 6 population-based case-control, & 7 hospital-based case-control).
List of included studies	Morgan (1974) Najem (1982) Mommsen (1982, 1983) Bravo (1987) Iscovich (1987) Brownson (1987) Risch (1988) Slattery (1988, 1988) Nomura (1989) Ross (1989) Mills (1991) D'Avanzo (1992) Chyou (1993) Murata (1986) Donato (1997) Bruemmer (1997)
Population	Cases of cancer of the bladder, urinary tract, or renal pelvis
Outcomes	Adjusted and unadjusted OR for current alcohol consumers vs non-drinkers, by gender, anatomical site, study design, measuring instrument, and sources of cases and controls.
Author's conclusions	Age and smoking adjusted OR 1.2 (95% CI 0.9-1.7) for 7 studies. Unadjusted OR 1.4 (95% CI 1.1-1.6) for 9 studies of men & women, OR 1.2 (95% CI 1.0-1.5) for 9 studies with men, OR 1.1 (95% CI 0.7-1.8) for 4 studies with women. For bladder carcinomas OR 1.3 (95% CI 1.1-1.5). Current alcohol consumption slightly increases the risk of male cancer of the urinary tract by approximately 30%, although not statistically significant. The risk of cancer of the urinary tract related to alcohol consumption for women and the influenced of the amount and type of alcohol remains unclear.

Reviewer's comment	No statistically significant association, except for bladder carcinomas. The authors estimated a total OR for "any use" when studies reported separate adjusted ORs for several consumption strata, using the exposure-specific prevalence of the non-cases as weights ie, did not investigate a dose-response relationship.

Author (year)	**Holman 1996**
Number & type of included studies [a]	Cohort, case-control, and cross-sectional studies were eligible for inclusion. Risk of mortality from 16 cohort studies and incidence of specific conditions from 132 epidemiological studies. In meta-analysis: Oropharyngeal: 4 studies Oesophageal: 7 studies Liver: 5 studies Laryngeal: 4 studies Female breast: 26 studies
List of included studies	Details of included studies not provided.
Population	Not specifically defined. Cases of 10 specific neoplastic, cardiovascular and alimentary conditions.
Outcomes	Pooled estimate of RR (95% CI) of incidence of cancer, according to usual alcohol intake (classified by NHMRC categories: responsible 0-2.9 drinks/day, hazardous 3-4.9 drinks/day, harmful 5+ drinks/day) compared with abstinence.
Author's conclusions	Oropharyngeal: responsible drinking RR 1.45 (95% CI 1.32, 1.60), hazardous drinking RR 1.85 (95% CI 1.49, 2.30), harmful drinking RR 5.39 (95% CI 4.67, 6.22) Oesophageal: responsible drinking RR 1.80 (95% CI 1.63, 1.99), hazardous drinking RR 2.37 (95% CI 2.03, 2.76), harmful drinking RR 4.26 (95% CI 3.70, 4.90) Liver: responsible drinking RR 1.45 (95% CI 1.09, 1.94), hazardous drinking RR 3.03 (95% CI 1.33, 6.92), harmful drinking RR 3.60 (95% CI 2.05, 6.32) Laryngeal: responsible drinking RR 1.83 (95% CI 1.51, 2.22), hazardous drinking RR 3.90 (95% CI 2.13, 7.13), harmful drinking RR 4.93 (95% CI 3.41, 7.15) Female breast: responsible drinking RR 1.09 (95% CI 1.06, 1.12), hazardous drinking RR 1.31 (95% CI 1.24, 1.39), harmful drinking RR 1.68 (95% CI 1.51, 1.87) The risk of cancers of the oropharynx, oesophagus, liver, larynx, and female breast increased with increasing alcohol intake level. Alcohol had adverse effects on these diseases even when the usual level of intake was classified as responsible.
Reviewer's comment	Literature search update of Holman *et al* (1990) Studies with baseline exposure contamination exceeding 0.25 drinks/day were excluded. Unclear whether RRs from individual studies were adjusted for smoking. Objective was to compare NHMRC recommendations on responsible, hazardous, and harmful alcohol intake with their effects on all-cause mortality and the occurrence of 10 specific diseases.

[a] In addition to neoplastic conditions, the study also evaluated the risk of neoplastic, cardiovascular and alimentary disease.

Author (year)	**Burzynski (1995)**
Number & type of included studies	29 studies (case-control and cohort) of cancers 15 different organ systems
List of included studies	Rosenberg (1990) Chu (1989) La Vecchia (1989) Toniolo (1989) Ewertz (1991) Franceschi (1991) Harvey (1987) Sneyd (1991) Howe (1991) Webster (1989) Licciardone (1989)

	Riboli (1991) Klatsky (1988) Cope (1991) De Stefani (1990) Longnecker (1990) Falk (1989) Brownson (1987) Luce (1988) Yu (1988) LaVecchia (1989) Blot (1988) Tuyns (1988) Merletti (1989) Brownson (1977) Nomura (1989) Bouchardy (1990) Farrow (1990) Yu (1988)
Population	Cancer cases
Outcomes	95% CIs for all studies, US studies, European studies, and 9 breast cancer studies.
Author's conclusions	For all 29 studies 95% CI 1.15, 1.28; for 13 US studies 95% CI 1.32, 1.55; for 16 European studies 95% CI 0.98, 1.14; 9 breast cancer studies 95% CI 1.07, 1.17. Data from the 29 studies suggests a weak association between drinking and cancer. However, it is not legitimate to draw any strong conclusions about the cause-and-effect relationships between consumption of alcoholic beverages and human cancer based upon the statistical summary reported. This study used only a simple mathematical summary of data currently extant on the carcinogenic risks of alcoholic beverages. A more discriminating combining of the data should be undertaken, which includes weighting factors based upon both quantitative data and qualitative judgments about the validity of each study.
Reviewer's comment	Literature search conducted in 1992. Very limited results reported. Other than a separate analysis of breast cancer, all cancers (from 15 organ systems) are combined to give a single estimate. It is unclear whether there was any adjustment for gender, smoking, etc.

Abbreviations: CI, confidence interval

Author (year)	**Longnecker 1994**
Number & type of included studies	38 studies 10 'follow-up' studies (?cohort) 28 case-control
List of included studies	Hiatt 1984 Hiatt 1988 Willett 1987 Schatzkin 1987 Harvey 1987 Paganini-Hill 1983 Byers 1982 Rohan 1988 Talamini 1984 Harris 1988 Le 1984 Begg 1983 Katsouyanni 1986i Van't Veer 1989 Young 1989 Chu 1989

	Rosenberg 1990 Schatzkin 1989 Toniolo 1989 Richardson 1989 Meara 1989 Adami 1988 Garfinkel 1988 Simon 1991 Metzger 1990 Reynolds 1988 La Vecchia 1989 Nasca 1990 Ewertz 1991 Sneyd 1991 Farraroni 1991 Longnecker 1992 Iscovich 1989 Miller 1978 Marubini 1989 Freidenreich 1993 Gapstur 1992
Population	Breast cancer cases
Outcomes	Breast cancer risk (mortality not reported)
Author's conclusions	RR (relative to non-drinkers): 1 drink/day: 1.11 (1.07, 1.16) 2 drinks/day: 1.24 (1.15, 1.34) 3 drinks/day: 1.38 (1.23, 1.55) The modest size of the association between alcohol and breast cancer] and the variation in results across studies leave the causal role of alcohol in question.
Reviewer's comment	Expected dose-response pattern is present, but of modest slope. Good quality, seminal review and meta-analysis.

Abbreviations: CI, confidence interval; RR, relative risk

Author (year)	**Roth 1994**
Number & type of included studies	38 case-control studies (from 30 publications)
List of included studies	Byers 1982 Rosenberg 1982 Begg 1983 Paganini-Hill 1983 Webster 1983 Le 1984 Talamini 1984 La Vecchia 1985 Harvey 1987 O'Connell 1987 Harris 1988 Rohan 1988 Chu 1989 Kato 1989 La Vecchia 1989 Richardson 1989 Toniolo 1989 Nasca 1990 Rosenberg 1990

	Sneyd 1991 Van't Veer 1989 Ferraroni 1991 Meara 1989 Adami 1988 Zaridze 1991 Harris 1992 Pawlega 1992 Young 1989 Ewertz 1991 Franceschi 1991
Population	Breast cancer cases
Outcomes	Breast cancer risk (mortality not reported)
Author's conclusions	Investigates impact of various study design characteristics upon breast cancer risk results (with respect to non-drinkers). Reports considerable difference between findings of studies with community-based and hospital-based controls (lower risk in community). This "casts even further doubt on the hypothesis concerning the causal nature of this reported relationship".
Reviewer's comment	Does not include cohort studies. Meta-analysed RR not reported (although slope of dose-response relationship is tabulated, grouped by study features in Table 4) Finding of differential of community and hospital controls suggests that measurement or selection bias may be at play.

Abbreviations: RR, relative risk

Author (year)	**Anderson (1993)**
Number & type of included studies	131 studies in total, 18 of which were excluded from the graphical analyses of RR.
List of included studies	*Cancer-related papers:* Kono (1986) Klatsky (1981) Tuyns (1988) Brugere (1986) Vincent (1963) Martinez (1969) Rothman (1972) Blot (1988) Keller (1965) Graham (1977) Bross (1976) Elwood (1984) Wynder (1957) Olsen (1985) Graham (1981) Brownson (1981) Hinds (1979) De Stefani (1987) Wynder (1956) Burch (1981) Herity (1982) Guenal (1988) Olsen (1985) Wynder (1961) Vassallo (1981) Pottern (1981) Victoria (1987)

	Tuyns (1977) Tuyns (1977) Tuyns (1983) Yu (1988) Pollack (1984) Gordon (1984) Hoey (1981) Hu (1988) Kabat (1986) Wynder (1967) Potter (1986) Miller (1983) Kune (1987) Klatsky (1988) Wu (1987) Hardell (1984) Oshima (1984) Stemhagen (1983) Yu (1988) Austin (1986) Yu (1983) Bulatao-Jayme (1982) Trichopoulos (1987) Wynder (1973) Falk (year not provided) Wynder (1983) Norell (1986) Hiatt (1988) Mack (1986) Gold (1985) Manousos (1981) Cuzick (1989) Raymond (1981) Schatzkin (1987) Willett (1987) Hiatt (1984) Hiatt (1988) Le (1984) Rohan (1988) Harvey (1987) Talamini (1984) La Vecchia (year not provided) O'Connell (1987) Paganini-Hill (1983) Harris (1988) Webster (year not provided) Byers (1982) Miller (1987) Begg (1983) Brownson (1987) Bravo (1987) Thomas (1983) Wynder (1963) Byers (1983) Gwinn (1986) Dyer (1980) Marmot (1981)

Population	Cases of cancers, liver disease, blood pressure, stroke, and cardiovascular disease. The cancers reported were stomach, colorectal, oesophageal, breast, liver, oral, pharyngeal, laryngeal, lung, bladder, ovarian.
Outcomes	RR of cancer incidence at 20, 40, 60, 80, and 100 g alcohol/day for cancers of the stomach, colon/rectum, oesophagus, breast, liver, oral, pharynx, larynx. Studies reporting relationship between alcohol and cancer-related mortality discussed (no analysis performed).
Author's conclusions	There is strong evidence of a dose-relationship between level of alcohol consumption and risk for cancers of the oropharynx, larynx, oesophagus, rectum (beer only), liver, and breast. A significant effect on total cancer mortality was found in four of five studies, two of which found a dose relationship. No evidence was found for an association between alcohol and cancers of the stomach, colon, pancreas (though two reports suggested an effect with beer drinking), lung, bladder, or ovaries (interestingly, alcohol may be protective in young women). The increased risk of breast cancer is consistent and convincing.
Reviewer's comment	Literature search dates not provided. Incidence reported graphically (RR vs grams of alcohol/day). 95% CIs not reported.

Abbreviations: CI, confidence interval; RR, relative risk

Author (year)	**Greenland & Longnecker, 1992**
Number & type of included studies	Methodological paper. Same data as Longnecker 1988, different methodology 38 studies (10 'follow-up' studies (?cohort), 28 case-control)
List of included studies	Hiatt Hiatt Willett Schatzkin Harvey Paganini-Hill Byers Rohan Talamini Harris Le Begg Katsouyanni Van't Veer Van't Veer Young Chu Rosenberg Schatzkin Toniolo Richardson Meara Meara Adami Garfinkel Simon Metzger Reynolds La Vecchia Nasca Ewertz Sneyd Farraroni

	Longnecker Iscovich Miller Marubini Freidenreich Gapstur
Population	Breast cancer cases
Outcomes	Breast cancer risk (mortality not reported)
Author's conclusions	Pooled estimate of slope coefficient, corrected for covariance of log relative risks: 0.00823 NB. Coefficient is the increase in log relative risk of breast cancer associated with average daily alcohol consumption of 1 gm.
Reviewer's comment	Methodological update of Longnecker 1988, but *superseded* by Longnecker 1994.

Author (year)	**Longnecker (1990)**
Number & type of included studies	27 studies (5 follow-up, 6 case-control with community controls, 15 case-control studies with hospital controls, 1 study with both hospital & community controls)
List of included studies	Pollack (1984) Klatsky (1988) Wu (1987) Garland (1985) Hirayama (1981) Kune (1987) Potter (1986) Martinez (1982) Graham (1988) Tuyns (1982) Fruedenheim (1988) La Vecchia (1988) Manousos (1983) Williams (1977) Kabat (1986) Maquart-Moulin (1986) Bristol (1985) Pickle (1984) Higginson (1966) Tajima (1985) Bjelke (1971) Dales (1979) Stocks (1957) Wynder (1969) Graham (1978) Wynder (1967) Miller (1983)
Population	Colorectal cancer cases
Outcomes	Relative risk of colorectal cancer for intake 24 g (2 drinks) of alcohol per day, by gender, cancer site, beverage type
Author's conclusions	RR of colorectal cancer 1.10 (95% CI 1.05-1.14) with consumption of 2 drinks per day Analysis by beverage type inconclusive, but stronger association with beer (RR 1.26, 95% CI 1.13-1.41), than wine (RR 1.11, 95% CI 0.91-1.36) or liquor (RR 1.13, 95% CI 0.99-1.29). The authors concluded that the data support a weak association between alcoholic beverage consumption and risk of colorectal cancer, which did not vary by gender or site within the bowel. Because the magnitude of the dose-response association was small, the findings regarding a causal role of alcoholic beverage consumption were inconclusive.
Reviewer's comment	Literature search 1966-March 1989. Outdated review.

Abbreviations: CI, confidence interval; RR, relative risk

Author (year)	Longnecker 1988
Number & type of included studies	16 studies 4 'follow-up' studies (?cohort) 12 case-control studies
List of included studies	Hiatt & Bawol, 1984 Hiatt 1988 Willett 1987 Schatzkin 1987 Harvey 1987 Rosenberg 1982 Webster 1983 Paganani-Hill & Ross 1983 Byers & Funch 1982 Rohan & McMichael 1988 Talamini 1984 O'Connell 1987 Harris & Wynder 1988 Le 1984 La Vecchia 1985 Begg 1983
Population	Breast cancer cases
Outcomes	Breast cancer risk (mortality not reported)
Author's conclusions	Relative to non-drinkers: RR of 24 g/day 1.4 (95% CI 1.0, 1.8) in case-control data RR of 24 g/day 1.7 (95% CI 1.4, 2.2) in follow-up data Authors state the evidence in favour of a dose-response relation between alcohol and breast cancer is compelling, however at lower levels of alcohol consumption the relative risk is not statistically significant (ie, <24 g/day).
Reviewer's comment	*Superseded* by Longnecker 1994

Abbreviations: CI, confidence interval; RR, relative risk

All 1,149 citations and abstracts (where available) were downloaded into *Reference Manager Version 10* and their content reviewed to identify any primary studies published since the key and supportive systematic reviews listed in **Table 5**.

APPENDIX 5: LITERATURE SEARCH FOR PIVOTAL NEW STUDIES

A literature search was conducted to identify any pivotal new studies published since the key systematic reviews for each of the specific cancer types specified within the scope of the current review. The search strategy is documented in **Table 48**.

Table 48 Search strategy and results for literature search for newer studies

Database (dates covered)	Search terms	Number of articles
EMBASE and Medline (<1966–2007) **(Searched on 26 Sep 2007 using EMBASE.com)**	**#1:** (('lung'/exp OR 'lung') OR ('liver'/exp OR 'liver') OR ('pancreas'/exp OR 'pancreas') OR pancreatic OR ('prostate'/exp OR 'prostate') OR prostatic OR ('ovary'/exp OR 'ovary') OR ovarian OR ovaries OR ('colon'/exp OR 'colon') OR colorectal OR ('rectum'/exp OR 'rectum') OR ('rectal'/exp OR 'rectal') OR ('oesophagus'/exp OR 'oesophagus') OR oesophageal OR esophageal OR ('pharynx'/exp OR 'pharynx') OR ('larynx'/exp OR 'larynx') OR ('oral'/exp OR 'oral') OR pharyngeal OR laryngeal OR 'aero-digestive') AND [2000-2007]/py	917,714
	#2: ('breast'/exp OR breast) AND [2004-2007]/py	66,842
	#3: #1 OR #2	963,481
	#4: ('cancer risk'/exp OR cancer/exp OR 'cancer incidence'/exp OR tumour/exp OR 'neoplasm'/exp OR 'tumour'/exp OR carcinogen/exp OR 'carcinogenic activity'/exp OR sarcoma/exp OR 'cancer epidemiology'/exp OR tumour* OR tumor* OR cancer* OR neoplas* OR malignan* OR carcino* OR *sarcoma) AND [2000-2007]/py	
	#5: 'alcohol'/mj AND [2000-2007]/py	13,618
	#6: #3 AND #4 AND #5	820
	#7: ('alcohol'/exp OR 'alcohol') OR alcohol*) AND [2000-2007]/py	105,517
	#8: 'carcinogenic activity'/mj OR 'cancer risk'/mj OR 'cancer incidence'/mj OR 'cancer epidemiology'/mj OR 'disease association'/mj OR 'risk factor'/mj AND [2000-2007]/py	7,728
	#9: #3 AND #7 AND #8	8,140
	#10: #6 OR #9	1,149
TOTAL		**1,149**