Ingezonden commentaren op het openbare concept van het achtergronddocument Alcoholhoudende dranken

De volgende organisaties hebben commentaar ingestuurd:

- Federatie Nederlandse Levensmiddelen Industrie
- Kennisinstituut Bier
- Nederlands Instituut voor Alcoholbeleid STAP
- Rijksinstituut voor Volksgezondheid en Milieu
- STIVA Stichting Verantwoorde Alcoholconsumptie
- Trimbos instituut
- Wereld Kanker Onderzoek Fonds

Van: Christine Grit
Verzonden: maandag 24 augustus 2015 15:55
Aan: GR_RGV2015
Onderwerp: EGV-015 020 A Respons op vijfde serie achtergronddocumenten Gezondheidsraad RGV 2015 definitief

Geachte mevrouw/heer

Bijgaand doe ik u de respons namens de FNLI toekomen in reactie op de vijfde reeks achtergronddocumenten van de Gezondheidsraad ten behoeve van het opstellen van de Richtlijnen goede voeding 2015.

Wij hopen dat u de in de respons opgenomen informatie kunt gebruiken.

Met vriendelijke groet,

Christine Grit
Manager Voeding & Gezondheid

FNLI

fnli.nl | voedingvooruit.nl | duurzamereten.nl | Twitter | LinkedIn

EGV-015 020 A Consultatie respons vijfde ronde achtergronddocumenten Gezondheidsraad - definitief

EGV 15 019 A
Notitie

Consultatierespons op 5 achtergronddocumenten

Onderwerp Achtergronddocumenten (1) Alcoholhoudende dranken, (2) Eiwit, (3) Kalium, (4) Transvetzuren en (5) Visvetzuren.

Datum | 24 augustus 2015

Inleiding
Als eerste willen we ook bij deze vijfde reeks achtergronddocumenten de Commissie bedanken voor het kunnen inzien van de Werkwijze en de achtergronddocumenten voor de Richtlijnen goede voeding (Rgv) 2015. Ook bij deze set documenten willen we graag de Commissie complimenteren met het vele werk dat hiertoe moet zijn uitgevoerd.

Het blijft voor ons lastig dat naarmate er meer documenten komen, het steeds onduidelijker wordt om overzicht te houden op de dwarsverbanden tussen voedingsstoffen, voedingssupplementen, voedingsmiddelen en voedingspatronen. Vaak duiken onderwerpen die (deels) al in een bepaald achtergronddocument zijn besproken ook op andere plaatsen op, soms wordt verwezen naar documenten en soms worden in het ene achtergronddocument andere getallen gehanteerd dan voor het andere terwijl deze gelijk zouden kunnen en moeten zijn.

Een ander punt dat ons zorgen blijft baren, is dat de keuze voor de top 10 van ziekten er toe bij kan dragen dat bepaalde voedingsgerelateerde aandoeningen niet of slechts heel beperkt zullen worden meegewogen bij het opstellen van de Richtlijnen. Terwijl hier sprake is van aandoeningen die weliswaar niet in de top 10 voorkomen maar wel degelijk grote gevolgen kunnen hebben voor de volksgezondheid en ook voor een deel kunnen worden voorkomen.

Terugkomend op de voedingsstoffen/levensmiddelen die in achtergronddocumenten überhaupt aan de orde komen (waarop wij dieper ingaan in onze respons op de eerste reeks achtergronddocumenten), is het onzes inziens een gemis dat er geen aandacht is voor plantensterolen en producten met toegevoegde plantensterolen. Zeker bij een exercitie waarin de preventie van hart- en vaatziekten en waarin het niveau van het LDL-cholesterol gehalte als een belangrijke intermediair is meegenomen, valt het op dat er geen aandacht voor is.

Los van deze algemene aandachtspunten die ons enige zorgen baren, maken we opnieuw graag van de gelegenheid gebruik om te reageren op de verschillende achtergronddocumenten die bij deze vijfde ronde zijn verspreid voor consultatie. Alle 5 de achtergronddocumenten zijn in onze achterban doorgenomen waarbij uiteraard de door de Commissie gestelde vragen zoveel mogelijk centraal hebben gestaan. De reacties op de verschillende documenten volgen vanaf pagina 3 van deze consultatierespons. De documenten worden in alfabetische volgorde behandeld, te beginnen bij 'Alcoholhoudende dranken' en eindigend bij 'Visvetzuren (Eicosapentaeenzuur en docosahexaeenzuur)'.

Voor de goede orde zij nog opgemerkt dat de aandachtspunten over de werkwijze die wij in de respons op de eerste reeks achtergronddocumenten hebben weergegeven, ook op deze reeks achtergronddocumenten van toepassing blijven.

Alcoholhoudende dranken

Opmerkingen
Het is ons niet duidelijk geworden wat nu precies sterke drank is. Zijn dat alle dranken met een bepaald minimum percentage aan alcohol (en welk percentage geldt dan)? Is daarbij gecorrigeerd voor de aanwezigheid van andere voedingsstoffen (zoals bijvoorbeeld suikers in likeurdranken)? Zijn in alle studies de definities hetzelfde?

Het is duidelijk bij de innamecijfers dat cider is meegeteld bij bier. Is de voedingswaarde echter gelijk afgezien van het alcoholgehalte? Is er rekening mee gehouden dat sommige bieren hogere gehaltes aan alcohol hebben dan andere? We vragen ons bovendien af in hoeverre het meetellen van versterkte wijnen zoals port en sherry bij "wijn" de resultaten niet zullen vertekenen. Daarbij komt dan nog dat onduidelijk is of in de studies dezelfde dranken steeds zijn meegeteld als is weergegeven in de tabel met wat in Nederland wordt gedronken.

Als laatste vragen we ons af in hoeverre bepaalde mixdrankjes zijn meegenomen in het achtergronddocument. Qua hoeveelheid alcohol per 100 gram bevinden deze zich dichter in de buurt van de wijnen dan de sterke drank hoewel ze vaak met sterke drank worden gemaakt.

Van: Ivonne Sleutels
Verzonden: vrijdag 21 augustus 2015 11:01
Aan: Javanmardi, M. (Mitra)
CC: Schoten, E.J. (Eert); Allers, J.M.; GR_Webmaster; Aafje Sierksma
Onderwerp: Re: Vijfde commentaarronde Richtlijnen goede voeding 2015

Geachte heer, mevrouw,

In de bijlage vindt u het commentaar van dr. ir. Aafje Sierksma, directeur Kennisinstituut Bier op het achtergronddocument over alcoholhoudende dranken.

Zou u kunnen bevestigen dat u dit document in goed orde hebt ontvangen?

Met vriendelijke groet,
Ir. Ivonne Sleutels
Communicatiemedewerker

Kennisinstituut Bier
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Aan de Gezondheidsraad

kennis instituut bier

Wageningen, 21 augustus 2015

Geachte Gezondheidsraad,

Graag stuur ik u ons commentaar op uw document 'Concept –Achtergronddocument Richtlijnen goede voeding 2015 – Alcoholhoudende dranken'.

Allereerst wil ik aangeven dat het eerdere document: 'Concept –Achtergronddocument Richtlijnen goede voeding 2015 – Alcohol' over het algemeen overeenkomt met onze interpretatie van de huidige wetenschappelijke stand van zaken. Het huidige achtergronddocument (Alcoholhoudende dranken) vertoont grote discrepanties met het achtergronddocument Alcohol. Dit is overigens niet verrassend omdat de epidemiologie niet in staat is drankspecifieke verschillen goed uit elkaar te trekken. Redenen hiervoor zijn de verschillen tussen een bier- en een wijndrinker die veelal niet worden meegewogen (een belangrijke factor is dieet) en het feit dat mensen nauwelijks alleen bier of alleen wijn drinken.

We willen met onderstaand commentaar een constructieve bijdrage leveren aan het document 'Concept Achtergronddocument Richtlijnen goede voeding 2015 – Alcoholhoudende dranken'. Echter, gezien de genoemde punten en daarmee de zwakheden in het onderzoek naar drankspecifieke effecten, adviseren wij dat u in overweging

neemt om op basis van de huidige wetenschappelijke kennis geen onderscheid te maken in alcoholhoudende dranken en het voedingsadvies te richten op alcoholconsumptie in het algemeen zoals in de vorige editie van de Richtlijnen goede voeding (2006) en zoals ook gedaan wordt in vele andere voedingsadviezen, zoals bijvoorbeeld die in de Dietary Guidelines for Americans, 2010.

Met vriendelijke groet,

Dr. Ir. Aafje Sierksma
Directeur Kennisinstituut Bier

Bijlage: Commentaar 1 t/m 3

Commentaar 1 (Interventieonderzoek):
Ondanks uw bewuste keuze voor de intermediairen (bloeddruk, LDL cholesterol en BMI), willen wij aangeven dat het in het geval van alcoholconsumptie ook relevant is om te kijken naar HDL cholesterol verhoging,[1] c.q. HDL gemedieerde cholesterol efflux[2] en ook zijn andere beschermende functies.[3-6] Daarnaast zijn er nog een aantal andere belangrijke factoren die een causaal verband aannemelijk maken, zoals fibrinogeen[1] en HbA1c[7] niet geëvalueerd. In al deze onderzoeken wordt geen onderscheid gevonden tussen alcoholhoudende dranken, waarmee dus gesuggereerd wordt dat het om een alcoholeffect gaat.
Interventieonderzoek maakt het zeer aannemelijk dat er een causaal verband is tussen matige alcoholconsumptie (dus geen drankspecifieke effecten) en een lagere incidentie van hart- en vaatziekten, zoals besproken in een systematisch review en meta-analyse[1] en cohort studies.[8]
Wat betreft effect op lichaamsgewicht is er in 2012 een meta-analyse verschenen van Bendsen en collega's over de relatie bierconsumptie en obesitas.[9]

Commentaar 2 (Cohortonderzoek):
Bij **paragraaf 3.2.1 (Bier)** worden in de toelichting niet altijd de juiste percentages overgenomen. Zo moet in regel 167 'ongeveer 5 procent' vervangen worden door '6 procent' en in regel 174 '45 procent' vervangen door '47 procent' en in regel 180 '40 en 85 procent' vervangen worden door '41 en 86 procent'. In het artikel van Ferrari wordt terecht gewezen op het volgende: "In this study beer use displayed more apparent risk patterns than wine consumption, particularly in men. Although we believe that this finding is relevant, we call for cautious interpretations of these results, as the lifestyle profile of wine and beer drinkers is profoundly different." Hiervoor verwijzen wij door naar commentaar 3 waarin ingegaan wordt op de eetpatronen van bier-, wijn- en gedistilleerd drinkers.

Bij **paragraaf 3.3.1 (Bier)** wordt geconcludeerd dat een verband tussen bierconsumptie en het risico op hart- en vaatziekten onwaarschijnlijk is, terwijl in paragraaf 3.3.2 (Wijn) wel uitgebreid in wordt gegaan op de bevindingen uit het onderzoek van Constanzo wat betreft wijn en hart- en vaatziekten. Constanzo en collega's schrijven in hun artikel: "Unfortunately, the very limited data available about either beer or spirit consumption in relation to cardiovascular or total mortality, did not allow us to perform a fully meta-analytic investigation on the latter two beverages". Met dit gegeven is het ons inziens onredelijk om het verband tussen bierconsumptie en het risico op hart- en vaatziekten als onwaarschijnlijk aan te duiden. Ook omdat de auteurs in de discussie specifiek aangeven: "A previous meta-analysis had shown a clear inverse dose-effect curve against vascular events for wine but not for beer intake. Evidence from the current updated and extended meta-analysis confirms the significant reduction of overall vascular risk associated with wine consumption and shows, apparently for the first time, a similar J-shaped relationship between beer intake and cardiovascular risk. Moreover, the comparison of studies which included a parallel, separate evaluation of wine and beer consumption, indicates a similar protecting effect of either beverage against cardiovascular risk."

Bij **paragraaf 3.4 (Diabetes Melllitus type 2)** wordt ons inziens onterecht geconcludeerd dat bierdrinkende mannen een hoger risico hebben op diabetes mellitus type 2 dan mannen die geen bier drinken en dat er geen verband is gevonden bij vrouwen, en dat er alleen met wijnconsumptie een geringe risicoverlaging is op diabetes mellitus type 2. Wij worden gesterkt in onze mening door de overall conclusie van dit onderzoek, waarbij vooral wordt ingegaan op een alcoholeffect en niet drankspecifieke effecten en de discussie waarin wordt aangegeven dat mogelijk leefstijl (zoals dieet) het verschil verklaart tussen de bier- en de wijndrinker (zie ook toelichting bij commentaar 3):

"Amongst men, moderate alcohol consumption was nonsignificantly associated with a lower incidence of diabetes with a hazard ratio (HR) of 0.90 (95% CI: 0.78–1.05) for 6.1–12.0 versus 0.1– 6.0 g day), adjusted for dietary and diabetes risk factors. However, the lowest risk was observed at higher intakes of 24.1–96.0 g day) with an HR of 0.86 (95% CI: 0.75–0.98). Amongst women, moderate alcohol consumption was associated with a lower incidence of diabetes with a hazard ratio of 0.82 (95% CI: 0.72–0.92) for 6.1–12.0 g day) (P interaction gender <0.01)."

"The specific risk reduction associated with wine consumption, however, appears to contradict the findings of several mechanistic studies. It was previously shown that the reduced risk of diabetes with moderate alcohol consumption can be explained by increased adiponectin concentrations for 25–30%. However, randomized trials in study populations consuming a variety of alcoholic beverages could not detect a difference in the effects on adiponectin concentrations. This suggests that the underlying biological mechanism is most probably explained by alcohol itself. The specific risk reduction observed with wine could thus be attributed to other factors associated with wine consumption. Previous studies have shown that wine drinkers differ from drinkers of other beverages by consuming a healthier diet and being less likely to smoke. As men and women may also differ with regard to such health-related behaviours, as is seen in the different structure of confounders amongst men and women, this could in part explain the specific association observed for wine consumption and the different effects between men and women."

Paragraaf 3.6 Borstkanker: Het feit dat er in het achtergronddocument 'Alcohol' wel een grote bewijskracht wordt gevonden aangaande alcoholconsumptie en risico op borstkanker bij vrouwen, terwijl in het achtergronddocument Alcoholhoudende dranken voor geen van de alcoholhoudende dranken een eenduidige uitkomst wordt gevonden, is tegenstrijdig. Smith-Warner en collega's geven aan: The specific type of alcoholic beverage did not strongly influence risk estimates. Tjønneland en collega's concluderen: "This large European study supports previous findings that recent average alcohol intake, irrespectively of beverage type, increases the risk of breast cancer." Deze bevindingen sterken nogmaals onze overtuiging dat het gaat om een alcoholeffect en dat daarom een voedingsadvies op basis van alcoholconsumptie en niet gespecificeerd per drank de voorkeur heeft.

Commentaar 3: Bier-, wijn- en gedistilleerddrinkers en hun verschillen
Een belangrijke reden om geen onderscheid te maken tussen een bier-, wijn- en gedistilleerddrinker, is omdat deze nagenoeg niet bestaan. Er wordt nauwelijks alleen bier of alleen wijn of alleen gedistilleerd gedronken. Dit blijkt ook uit onderzoek van Sluik en collega's.[10] Zij hebben deelnemers aan de VCP 2007-2010 ingedeeld naar drankvoorkeur, waarbij als criterium is gebruikt dat als 70% van de consumptie bestond uit wijn, dan wel bier, dan wel gedistilleerd men respectievelijk een wijn, bier-, gedistilleerddrinker is. Als het aantal glazen bier, wijn of gedistilleerd niet optelde tot 70%, dan had men geen voorkeur. Op basis van deze, overigens niet officieel bestaande, definitie waren de drankvoorkeuren als volgt:

	Biervoorkeur	Wijnvoorkeur	Gedistilleerd voorkeur	Geen voorkeur	Geen alcohol
Man	32%	10%	5%	33%	20%
Vrouw	5%	26%	6%	22%	41%

Verder hebben Sluik en collega's in hetzelfde onderzoek gekeken naar de eetpatronen van de op deze manier gedefinieerde bier-, wijn- en gedistilleerd drinkers.[11] Mensen met een voorkeur voor bier hadden ongezondere eetgewoonten dan mensen met een voorkeur voor wijn. Hierdoor is het dus niet uitgesloten dat dieet een confounder is in de relatie tussen alcoholconsumptie en gezondheid, waarvoor veelal niet wordt gecorrigeerd. Dat zou een reden kunnen zijn dat de zogenoemde bierdrinkers er daarom "slechter" vanaf komen dan de zogenoemde wijndrinkers.
Ook uit een systematische review door Sluik en collega's blijkt dat drankvoorkeur gerelateerd is aan eetgewoonten.[11] Zij concluderen dat als er specifiek naar drankvoorkeur gekeken wordt in relatie tot gezondheid, voeding zeker moet worden meegenomen als confounder aangezien onderliggende voedingsvoorkeuren vaak eerder gerelateerd zijn aan gezondheid dan het type drank.

Referenties

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6. van der Gaag, M. S. et al. Alcohol consumption stimulates early steps in reverse cholesterol transport. Journal of lipid research 42, 2077-2083 (2001).
7. Schrieks, I.C. et al. The effect of alcohol consumption on insulin sensitivity and glycemic status: a systematic review and meta-analysis of intervention studies. Diabetes Care 38, 723-732 (2015).
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11. Sluik, D. et al. Alcoholic Beverage Preference and Dietary Habits: A Systematic Literature Review. Crit Rev Food Sci Nutr 15 Feb 12:0 (2015).

NEDERLANDS
INSTITUUT
VOOR ALCOHOLBELEID

Utrecht, 21 augustus 2015

Hierbij ontvangt u de tweede reactie (nu als onderdeel van de vijfde commentaarronde) van het Nederlands Instituut voor Alcoholbeleid STAP op het concept rapport ' **Achtergronddocument Richtlijnen goede voeding 2015, deelstudie Alcoholhoudende dranken'.**

1. Wij hebben ernstige twijfels bij de conclusie in het rapport dat er geen eenduidig verband zou bestaan tussen alcoholgebruik en het ontstaan van borstkanker bij vrouwen. In de bijlage bij deze reactie sturen we twee recente artikelen mee waarin duidelijke uitspraken worden gedaan over de samenhang tussen alcoholgebruik en het ontstaan van borstkanker en waarbij geen sprake is van het ontbreken van een eenduidig verband.
2. Wat ons verontrust is dat in uw rapport steeds nadrukkelijk onderscheid wordt gemaakt tussen wat bekend is over de relatie tussen borstkanker (en ook in geval van andere ziekten) en wijngebruik, borstkanker en biergebruik en borstkanker en het gebruik van sterke drank. En dat terwijl algemeen bekend is dat het primair gaat om de relatie tussen het gebruik van alcohol als carcinogene stof en het ontstaan van diverse ziekten waaronder kanker. Het kan niet zo zijn dat we als resultaat van uw rapport gaan zien dat de diverse soorten alcoholhoudende drank wat de risico's van het gebruik ervan betreft, tegen elkaar uitgespeeld worden. terwijl de kern is dat de alcohol die deze dranken bevatten als zodanig de belangrijkste factor die bepalend is voor de risico's. Ik vraag u tenminste een apart hoofdstuk te wijden aan de samenhang tussen de besproken ziekten en het gebruik van alcohol zonder daarbij onderscheid te maken tussen de diverse verschijningsvormen van alcohol. Dit mede gezien het feit dat er hoe langer hoe meer tussenproducten geconsumeerd worden, zoals Desperados (bier met Tequila), en Muscat (wijn met een scheutje gedistilleerde alcohol). .
3. Ik stuur u nogmaals het CUP rapport van het WCRF over borstkanker en de twee zeer recente artikelen van studies die het verband tussen **alcohol** en borstkanker eenduidig aantonen.

Het betreft de artikelen:

Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition
Auteurs: Isabelle Romieu, Chiara Scoccianti, Veronique Chaje`s, Jordi de Batlle, Carine Biessy, Laure Dossus, Laura Baglietto, Francoise Clavel-Chapelon, Kim Overvad, Anja Olsen, Anne Tjønneland, Rudolf Kaaks, Annekatrin Lukanova, Heiner Boeing, Antonia Trichopoulou, Pagona Lagiou, Dimitrios Trichopoulos, Domenico Palli, Sabina Sieri, Rosario Tumino, Paolo Vineis, Salvatore Panico, H. B(as) Bueno-de-Mesquita, Carla H. van Gils, Petra H. Peeters, Eiliv Lund, Guri Skeie, Elisabete Weiderpass, Jose Ram_on Quiros Garc, Maria-Dolores Chirlaque, Eva Ardanaz, Maria-Jose Sanchez, Eric J. Duell, Pilar Amiano, Signe Borgquist, Elisabet Wirf, Goran Hallmans,Ingegerd Johansson,Lena Maria Nilsson, Kay-Tee Khaw, Nick Wareham, Timothy J. Key, Ruth C. Travis, Neil Murphy, Petra A. Wark, Pietro Ferrari and Elio Riboli
Gepubliceerd in: Int. J. Cancer: 137, (2015) 1921–1930

en

Light to moderate intake of alcohol, drinking patterns, and risk of cancer: results from two prospective US cohort studies
Auteurs: Yin Cao, Walter C Willett, Eric B Rimm, Meir J Stampfer, Edward L Giovannucci
Gepubliceerd in: British Medical Journal: (2015), 351-h4238.

Hoogachtend,

Ir. Wim van Dalen

Nederlands Instituut voor Alcoholbeleid STAP
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World Cancer Research Fund

American Institute for Cancer Research

Continuous Update Project

Keeping the science current

Breast Cancer 2010 Report

Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer

Continuous Update Project

CUP

WORLD CANCER RESEARCH FUND GLOBAL NETWORK

OUR VISION

The World Cancer Research Fund global network helps people make choices that reduce their chances of developing cancer.

OUR HERITAGE

We were the first cancer charity:

- To create awareness of the relationship between diet and cancer risk
- To focus funding on research into diet and cancer prevention
- To consolidate and interpret global research to create a practical message on cancer prevention

OUR MISSION

Today the World Cancer Research Fund global network continues:

- Funding research on the relationship of nutrition, physical activity and weight management to cancer risk
- Interpreting the accumulated scientific literature in the field
- Educating people about choices they can make to reduce their chances of developing cancer

THE WCRF GLOBAL NETWORK

The World Cancer Research Fund (WCRF) global network comprises WCRF International, which operates as the umbrella association for the global network's four charitable organisations: The American Institute for Cancer Research (AICR); World Cancer Research Fund (WCRF UK); World Cancer Research Fund Netherlands (WCRF NL); World Cancer Research Fund Hong Kong (WCRF HK).

Please cite the Report as follows:
World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. 2010

This Report provides an updated version of section 7.10 Breast Cancer from the Second Expert Report: Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. This section has been updated with the latest information from the 2008 Continuous Update Project Breast Cancer SLR prepared by a team at Imperial College London, UK (see acknowledgements). For further details on the epidemiological evidence please see the full 2008 Continuous Update Project Breast Cancer SLR (Second Expert Report). For further details on mechanisms please see the Second Expert Report.

The First and Second Expert Reports represent the most extensive analysis of the existing science on the subject to date. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project, in collaboration with Imperial College London. The Continuous Update Project builds upon the work conducted for the Second Expert Report and began by merging all the databases from the different cancer sites into an upgraded database.

The Continuous Update Project provides the scientific community with a comprehensive and up to date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It also provides an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's cancer prevention recommendations based on the 2007 Expert Report.

In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the Continuous Update Project systematically reviews the science. WCRF/AICR has convened a panel of experts (the Continuous Update Project Panel (see acknowledgements) consisting of leading scientists in the field of diet, physical activity, obesity and cancer who consider the evidence produced by the systematic literature reviews and meta-analyses, and consider the results and draw conclusions before making recommendations.

The updates to the SLRs are being conducted by a team of scientists at Imperial College London in liaison with the SLR centres where possible.

Instead of periodically repeating the extensive task of conducting multiple systematic literature reviews that cover a long period of time, the continuous review process is based on a live system of scientific data that is updated on an ongoing basis from which, at any point in time, the most current review and meta-analysis of scientific data can be performed.

Periodically WCRF/AICR will produce reports which will outline the scientific developments in the field of diet, physical activity, obesity and cancer. The reports may also include updates to the WCRF/AICR recommendations.

The updated recommendations will be used by the WCRF/AICR education and media relation departments to inform the general public both of the benefits of a healthy lifestyle and of the developments in science that underpin these recommendations.

New information in this report

Section 1. Updated with recent mortality and survival data.

Section 2. Updated section on family history

Section 3. No update

Section 4. No update

Section 5. A new section briefly describing the methodology of the Continuous Update Project

Section 6. Evidence has been updated based on the 2008 Continuous Update Project Breast Cancer SLR and judgements from the Continuous Update Project Panel

Section 7. Provides a comparison with the Second Expert Report.

Since publication of this report in 2011, some changes have been made to the design and formatting, but no changes have been made to the content of the report or Panel conclusions. Please note, however, that the Second Expert Report matrix in this report has been replaced with the Continuous Update Project Matrix (on page 3).

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (PREMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks
Probable	Body fatness	Adult attained height[1] Greater birth weight
Limited - suggestive	Physical activity[2]	
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; total fat; folate; vitamin D; calcium; glycaemic index; dietary patterns; adult weight gain; abdominal fatness	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
2 Physical activity of all types: occupational, household, transport and recreational.

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (POSTMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks Body fatness Adult attained height[1]
Probable	Physical activity[2]	Abdominal fatness Adult weight gain
Limited - suggestive		Total fat
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; folate; vitamin D; calcium; selenium; glycaemic index; dietary patterns; birth weight; energy intake	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
2 Physical activity of all types: occupational, household, transport and recreational.

Cancer of the breast is the most common cancer in women worldwide. Around 1.1 million cases were recorded in 2004.

Observed rates of this cancer increase with industrialisation and urbanisation, and also with facilities for early detection. It remains much more common in high-income countries but is now increasing rapidly in middle- and low-income countries, including within Africa, much of Asia, and Latin America. Breast cancer is fatal in under half of all cases and is the leading cause of death from cancer in women (fifth for men and women combined), accounting for 16 per cent of all cancer deaths worldwide in 2004.

Breast cancer is hormone related, and the factors that modify risk of this cancer when diagnosed premenopausally and when diagnosed postmenopausally (much more common) are not the same.

The Continuous Update Project Panel judges as follows:
The evidence that lactation protects against breast cancer at all ages is convincing.

Physical activity probably protects against breast cancer postmenopause, and there is limited evidence suggesting that it protects against this cancer diagnosed premenopause. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing, and these are probably also a cause of breast cancer diagnosed premenopause.

The factors that lead to greater birth weight, or its consequences, are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably also a cause. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

Life events that protect against breast cancer include late menarche, early pregnancy, bearing children, and early menopause, all of which have the effect of reducing the number of menstrual cycles, and therefore lifetime exposure to oestrogen. The reverse also applies.

See chapter 8 of the Second Expert Report for evidence and judgements on factors that modify risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable" show that lactation protects against breast cancer; that alcoholic drinks are a cause of this cancer; that the factors that lead to a greater adult attained height, or its consequences, are a cause of postmenopausal and probably also premenopausal breast cancer; that factors leading to greater birth weight, or its consequences, are

probably a cause of premenopausal breast cancer; and that abdominal body fatness and adult weight gain are probably a cause of postmenopausal breast cancer. Body fatness is a cause of postmenopausal breast cancer but probably protects against premenopausal breast cancer.

Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts, and connective tissue. Breast tissue develops in response to hormones such as oestrogens, progesterone, insulin and growth factors. The main periods of development are during puberty, pregnancy, and lactation. The glandular tissue atrophies after menopause.

Breast cancers are almost all carcinomas of the epithelial cells lining the ducts (the channels in the breast that carry milk to the nipple).[1] Premenopausal and postmenopausal breast cancers are considered separately in this Report. Although rare (less than 1 per cent of cases [2]), breast cancer can occur in men, but it is not included here.

1. Trends, incidence, and survival

Breast cancer is the most common cancer in women in high-, middle- and low-income countries.[3] Age-adjusted rates of breast cancer in women are increasing in most countries, particularly in areas where the incidence had previously been low, such as Japan, China and south-eastern and eastern Europe.[4, 5]

This is predominately a disease of high-income countries where overall rates are nearly three times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from 75-100 per 100 000 women in North America, northern Europe, and Australia, to less than 20 per 100 000 in parts of Africa and Asia. [6] In the USA, rates are higher among white women than those from other ethnic groups, although mortality is highest in black women.[7]

Overall risk doubles each decade until the menopause, when the increase slows down or remains stable. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk assume the rate in the host country within one or two generations. This shows that environmental factors are important in the progression of the disease.[8]

Breast cancers can often be detected at a relatively early stage. In countries that provide or advocate screening, most of these cancers are diagnosed when the disease is still at a localised stage.[9] Survival rates range from 90 to less than 50 per cent, depending on the characteristics of the tumour, its size and spread, and the availability of treatment.[10] Average 5-year survival rates are more than 80% in North America, Sweden, Japan, Finland and Australia compared with less than 60 per cent in Brazil and Slovakia and less than 40 per cent in Algeria.[11] The low survival rate in middle- and low-income countries can be explained mainly by a lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by a lack of adequate diagnosis and treatment facilities. Breast cancer accounts for nearly 23 per cent of all cancer incidence in women and 16 per cent of all cancer deaths (all sites except for skin (non-melanoma) and in women only). [3, 6] Breast cancer is the ninth most common cause of death in high income countries and around 69% of all breast cancer deaths occur in middle- and low-income countries.[3] Mortality rates have remained fairly stable between 1960 and 1990 in most of Europe and the Americas; and

have since showed a decline, which has reached 25-30% in northern Europe.[12] See box 1.

Box 1 cancer incidence and survival
The cancer incidence rates and figures given in this Report are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries; regions of some countries have few or no records; records in countries suffering war or other disruption are bound to be incomplete; and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is higher than the figures given here. The cancer survival rates given in this chapter and elsewhere are usually overall global averages. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer and well established treatment facilities. Survival also is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some internal cancers are often evident only at a late stage, which accounts for relatively low survival rates. In this context, 'survival' means that the person with diagnosed cancer has not died 5 years after diagnosis.

2. Pathogenesis

Breast tissue, as well as hormones and hormone-receptor status, varies at different stages of life. It is therefore possible that individual risk factors will have different effects at different life stages (see 6. Evidence and Judgements). Early menarche, late menopause, not bearing children, and late (over 30) first pregnancy all increase breast cancer risk.[8, 13] The age when breasts develop, and menopause, are both influenced by nutrition, with overnutrition leading to early puberty and late menopause; undernutrition delays puberty and advances menopause (see chapter 6.2 Second Expert Report).

Hormones play an important role in breast cancer progression because they modulate the structure and growth of epithelial tumour cells.[10] Different cancers vary in hormone sensitivity. Many breast cancers also produce hormones, such as growth factors, that act locally, and these can both stimulate and inhibit the tumour's growth.[14, 15]

Family history of breast cancer is associated with a 2-3 fold higher risk of the disease. Some mutations, particularly in BRCA1, BRAC2 and p53 result in a very high risk of breast cancer. These mutations are rare and account for only 2 to 5 per cent of total cases.[16] In addition, growth factor receptor genes, as well as some oncogenes, are overexpressed in many breast cancers.[10] (Also see box 2.2. chapter 2, Second Expert Report).

3. Other established causes

3.1 General

This section lists factors outside the scope of this Report, identified as established causes of cancer by the World Health Organization International Agency for Research on Cancer, and other authoritative bodies. These factors are listed in Chapter 2.4 of the Second Expert Report: tobacco use; infectious agents; radiation; industrial chemicals; and some medications. Other diseases may also increase the risk of cancer. In the same way, life events that modify the risk of cancer – causative and protective – are also included.

'Established' effectively means 'beyond reasonable doubt' – roughly the equivalent of the judgement of 'convincing' used in this Report. Occasionally, authorative findings that perhaps fall short of 'established' are also included here.

Where possible, a note of interactive or multiplicative effects with food, nutrition, and the other factors covered by this Report is added, as is any indication of scale or relative importance. The factors here are almost all causative, whereas much of the evidence on food, nutrition, physical activity, and related factors shows or suggests protection against cancer.

3.2 Specific

Life events. Lifetime exposure to oestrogen, influenced by early menarche, late natural menopause, not bearing children, and late (over 30) first pregnancy all increase the risk of, and may be seen as causes of, breast cancer.[8, 13] The reverse also applies: late menarche, early menopause, bearing children, and early pregnancy all reduce the risk of, and may be seen as protective against breast cancer. Age of breast development and menopause are influenced by nutrition, with high-energy diets promoting earlier puberty and late menopause, and low-energy diets delaying puberty and advancing menopause.

Radiation. Ionising radiation exposure from medical treatment such as X-rays, particularly during puberty, increases risk, even at low doses.[17]

Medication. Hormone replacement therapy is a cause of breast cancer. The increased risk appears to disappear a few years after cessation.[18] Oral contraceptives containing both oestrogen and progesterone cause a small, transient, increased risk of breast cancer; the increased risk disappears after cessation.[19]

4. Interpretation of the evidence specific to breast cancer

4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7 of the Second Expert Report.

'Relative risk' is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.2 Specific

Considerations specific to breast cancer include:

Patterns. The preponderance of data from high-income countries is a special issue with breast cancer. Breast cancer is hormone related, and factors that modify risk have different effects on cancers diagnosed pre- and postmenopause.

Classification. Because of the importance of menopause as an effect modifier, studies should stratify for menopause status. Many do not.

Confounding. Hormone replacement therapy is an important possible confounder in postmenopausal breast cancer. A few studies also reported results separately for different hormone receptor profiles within cancers. High-quality studies adjust for age, number of reproductive cycles, age at which children were born, and the taking of hormone-based medications.

Effect modification. There is growing evidence that the impact of dietary exposures on risk of breast cancer may differ according to the particular molecular subtypes of cancer.

5. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report much of the methodology following for the Continuous Update Project remains unchanged from that used previously. Based upon the experience of conducting the systematic literature reviews for the Second Expert Report some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case-control studies. The 2008 Continuous Update Project Breast Cancer SLR included studies published up to December 2007. Publications in foreign languages were not included. Due to the large number of cohort studies, analysis and interpretation of case-control studies was not included in the Continuous Update Project SLR. Meta-analyses and forest plots of highest versus lowest categories were prepared for breast cancer incidence. Studies with mortality endpoints previously included in analyses were removed. Studies reporting mean difference as a measure of association are not included in the Continuous Update Project SLR as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies. (For more information on methodology see the full 2008 Continuous Update Project Breast Cancer SLR (Second Expert Report).

6. Evidence and judgements

The updated search identified 81 new articles, giving a total of 954 publications for breast cancer. The following sections include evidence from case-control studies considered as part of the Second Expert Report; however as mentioned in the previous section the evidence from case-control studies was not included in the 2008 Continuous Update Project Breast Cancer SLR. Fuller summaries of the experimental and mechanistic evidence can be found in chapters 4-6 of the Second Expert Report. For information on the criteria for grading the evidence see box 3.8 of the Second Expert Report. References to studies added in the Continuous Update Project have been included in the following sections; for details on references to other studies see Second Expert Report.

6.1 Alcoholic drinks

(Also see sections 3.7.1 Alcoholic drinks and 5.4 Alcohol (as ethanol) of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 4 new cohort studies[20-23] that investigated alcoholic drinks and 2 new cohort studies[24, 25] and 3 recent publications from previously included cohort studies[26-28] that investigated ethanol intake. For premenopausal breast cancer a total of 4 cohort studies investigated alcoholic drinks and 6 cohort studies investigated ethanol intake. The respective numbers for postmenopausal breast cancer were 9 and 16. For all-age breast cancer a total of 13 cohort studies investigated alcoholic drinks and 11 cohort studies investigated ethanol intake. Most studies showed increased risk with increased intake. Meta-analysis of cohort studies for the Second Expert Report showed a 10 per cent increased risk for all-age breast cancer, a 9 per cent increased risk for premenopausal breast cancer and a 8 per cent increased risk for postmenopausal breast cancer per 10 g ethanol (Page 167 Second Expert Report). An updated meta-analysis for postmenopausal breast cancer

showed an 8 per cent increased risk per 10 g ethanol (Figure A1 2008 Continuous Update Project Breast Cancer SLR). The Second Expert Report included 31 case-control studies that investigated alcoholic drinks and 29 case-control studies that investigated ethanol intake and all-age breast cancer. Meta-analysis of case-control data showed a 5 per cent increased risk per 5 drinks/week, and a 6 per cent increased risk per 10 g ethanol/day (Pages 166-167 Second Expert Report). Menopausal status did not significantly alter the association.

Two pooled analyses also showed statistically significant increased risks of 9 and 7 per cent per 10 g ethanol/day. The first was based on 6 cohort studies with more than 320 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases. The other analysed 53 case-control studies, with more than 58 000 cases and more than 95 000 controls.[29, 30] A meta-analysis of 3 cohort and 7 case-control studies assessed the association between alcohol intake and the risk of ER-/PR-defined breast cancer. [31] The dose-response meta-analysis showed that an increase in alcohol consumption of 10 g of ethanol per day was associated with statistically significant increased risks for all ER+ (12 per cent), all ER- (7 per cent), ER+PR+ (11 per cent) and ER+PR- (15 per cent), but not ER-PR-. A statistically significant heterogeneity of the results across all ER+ *versus* ER-PR- was observed.

Reactive metabolites of alcohol, such as acetaldehyde, may be carcinogenic. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. High consumers of alcohol may have diets deficient in essential nutrients, making tissues susceptible to carcinogenesis. In addition, most experimental studies in animals have shown that alcohol intake is associated with increased breast cancer risk. Alcohol interferes with oestrogen metabolism and action in multiple ways, influencing hormone levels and oestrogen receptors.

There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status partially mitigates the risk from increased alcohol consumption.[32]

The evidence added for the Continuous Update Project is consistent with that from the Second Expert Report. There is ample and generally consistent evidence from cohort and case-control studies.

A dose-response relationship is apparent. There is robust evidence for mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing. No threshold was identified.

6.2 Lactation

(Also see section 1.6.1 Breastfeeding of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 2 new cohort studies[33, 34] that investigated ever having breastfed as compared with never having breastfed and 3 new cohort studies[20, 21, 33] that investigated the total duration of lactation. For each of premenopausal and postmenopausal breast cancer a total of 2 cohort studies investigated ever having breastfed compared to never having breastfed and 2 cohort studies investigated total duration of lactation. For all-age breast cancer 3 studies investigated ever having breastfed and 6 studies investigated total duration of lactation. The Second Expert Report included 37 case-control studies that investigated ever having breastfed as compared with never having breastfed and 55 case-control studies that investigated the total duration of lactation. Most cohort and case-control studies reported decreased risk with ever having breastfed and with increasing duration of breastfeeding. Previous meta-analyses from the Second Expert Report for case-control data showed a 2 per cent decreased risk per 5 months of total breastfeeding; and for cohort data showed a non-significant decreased risk (Page 241 Second Expert Report). Pooled analysis from 47 epidemiological studies in 30 countries (more than 50 000 controls and nearly 97 000 breast cancer cases) showed a statistically significant decreased risk of breast cancer of 4.3 per cent for each 12 months of breastfeeding. Menopause status was not an effect modifier.[35] The relationship between breastfeeding and breast cancer according to hormone receptor status was investigated in a meta-analysis of 5 population-based case-control studies. A statistically significantly lower risk was found, both of ER+/PR+ breast cancers

(22 per cent) and for ER-/PR- cancers (26 per cent), for more than 6 months of breastfeeding compared with never breastfeeding. [36]

Lactation is associated with increased differentiation of breast cells and with lower exposure to endogenous sex hormones during amenorrhea accompanying lactation. In addition, the strong exfoliation of breast tissue during lactation, and the massive epithelial apoptosis at the end of lactation, could decrease risk by elimination of cells with potential DNA damage.

The evidence added for the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant epidemiological evidence from both cohort and case-control studies, which is consistent and shows a dose-response relationship. There is robust evidence for plausible mechanisms that operate in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that lactation protects against both premenopausal and postmenopausal breast cancer is convincing.

6.3 Physical activity

(Also see section 6. Physical Activity of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 2 new cohort studies[37, 38] investigating total physical activity; 1 new cohort study investigating occupational activity[37]; 3 new cohort studies[37-39] and 1 recent publication from a previously included cohort study[40] investigating recreational activity; and 2 new cohort studies[37, 38] investigating household activity. For premenopausal breast cancer a total of 5 cohort studies investigated total physical activity and 4, 3 and 1 studies investigated occupational, recreational and household activities respectively. For postmenopausal breast cancer 2 studies investigated total activity and 5, 11 and 1 studies investigated occupational, recreational and household activities respectively. For all-age breast cancer 4 studies investigated total physical activity and 4, 5 and 1 studies investigated occupational, recreational and household activities respectively. The Second Expert Report included 8 case-control studies that investigated total physical activity, 7 case-control studies that investigated occupational activity and 11 case-control studies that investigated recreational activity.

Menopause age unspecified

Most studies showed decreased risk with increased physical activity. Meta-analysis of case-control studies for the Second Expert Report showed a 10 per cent decreased risk per 7 MET-hours recreational activity/ week (Page 204 Second Expert Report).

Premenopause

Data were inconsistent for cohort studies for physical activity; however most case-control studies reviewed for the Second Expert Report showed evidence of decreased risk (Page 204 Second Expert Report).

Postmenopause

Nearly all of the cohort studies showed decreased risk with increased physical activity. The meta-analyses from the Second Expert Report of cohort and case-

control data both showed a 3 per cent decreased risk per 7 MET-hours recreational activity/week (Page 205 Second Expert Report).

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, it decreases levels of oestrogens and androgens in postmenopausal women. Some trials have also shown decreases in circulating oestrogens, increased menstrual cycle length, and decreased ovulation in premenopausal women with a high level of physical activity.

Premenopause: There is ample evidence from prospective studies, but it is inconsistent. There is evidence from case-control studies suggestive of a decreased risk with higher levels of physical activity. The conclusion reached for the Second Expert Report remains unchanged. There is limited evidence suggesting that physical activity protects against premenopausal breast cancer.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is ample evidence from prospective studies showing lower risk of postmenopausal breast cancer with higher levels of physical activity, with a dose-response relationship, although there is some heterogeneity. There is little evidence on frequency, duration, or intensity of activity. The conclusion reached for the Second Expert Report remains unchanged. There is robust evidence for mechanisms operating in humans. Physical activity probably protects against postmenopausal breast cancer.

6.4 Body fatness

(Also see section 8.1.1 Body Mass Index of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 10 new[34, 41-49] and 2 recent publications from previously included studies[39, 50] investigating body fatness, as measured by BMI for pre- and postmenopausal breast cancer. For premenopausal breast cancer there was a total of 22 studies and for postmenopausal breast cancer there were 28 studies. The Second Expert Report included more than 100 case-control studies that investigated body fatness. When grouped for all ages the Second Expert Report showed that the data were inconsistent in relationship to body fatness (Page 218 Second Expert Report) and this remained true for the Continuous Update Project. However, a consistent effect emerged when they were stratified according to menopausal status.

Premenopause

Most studies showed a decreased risk for premenopausal breast cancer. Meta-analyses for the Second Expert Report (Page 221 Second Expert Report) showed a 15 per cent decreased risk per 5kg/m^2 for cohort studies and an 8 per cent decreased risk per 5kg/m^2 for case-control studies; the updated meta-analysis for

cohort studies showed a 7 per cent decreased risk per 5kg/m^2 (Figure BMI4 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of four cohort studies with 723 cases of premenopausal breast cancer followed up for up to 11 years showed a 14 per cent decreased risk per 5kg/m^2.[51] A meta-analysis of 20 cohort studies reported an 8 per cent decreased risk per 5kg/m^2.[52]

Postmenopause

Most studies showed an increased risk for postmenopausal breast cancer with increased body fatness. Meta-analysis of cohort studies for the Second Expert Report (Page 219 Second Expert Report) showed an 8 per cent increased risk per 5kg/m^2 and a 13 per cent increased risk per 5kg/m^2; the updated meta-analysis of cohort studies showed a 13 per cent increased risk per 5kg/m^2 (Figure BMI7 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of seven cohort studies with 3208 cases of postmenopausal breast cancer followed up for up to 11 years showed a 9 per cent increased risk per 5kg/m^2.[51] A meta-analysis of 31 cohort studies reported a 12 per cent increased risk per 5kg/m^2.[52]

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (programmed cell death). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3 Second Expert Report). Adjusting for serum levels of oestradiol diminishes or destroys the association with BMI, suggesting that hormones are a predominant mechanism.[53]

There is no single well established mechanism though which body fatness could prevent premenopausal breast cancer. According to the oestrogen plus progesterone theory, overweight premenopausal women would be protected because they would be more frequently anovulatory, and therefore less likely to be exposed to endogenous progesterone. However, this theory is not well supported by recent studies, which suggest that natural progesterone could be protective.[54] Normal levels of natural progesterone are likely to be protective, and well nourished, or perhaps overnourished women, who may become slightly overweight in adulthood, may be protected by their natural fertile condition. Another possible mechanism is that the increased adipose tissue-derived oestrogen levels in overweight children could induce early breast differentiation and eliminate some targets for malignant transformation.[55] Anovulation and abnormal hormone profiles are commonly associated with obesity.[56] The age-specific pattern of association of breast cancer with BMI, therefore, is largely explained by its relationship with endogenous sex hormone levels.

Breast cancer diagnosed after the menopause is much more common. Therefore, throughout life, a decreased risk of premenopausal breast cancer would be outweighed by an increased risk of postmenopausal breast cancer.

Premenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is a substantial amount of consistent evidence epidemiological evidence with a dose-response relationship, but the mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. Greater body fatness probably protects against premenopausal breast cancer.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant and consistent epidemiological evidence and a clear dose-response relationship with robust evidence for mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that greater body fatness is a cause of postmenopausal breast cancer is convincing.

6.5 Adult attained height

(Also see section 8.3.1 Height of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 5 new cohort studies[34, 39, 41, 48, 57] that investigated adult attained height. The total number of cohort studies was 21 for all-age or age unspecified, 17 for premenopausal and 22 for postmenopausal breast cancer. The Second Expert Report included 29 case-control studies that investigated adult attained height and all-age breast cancer, 38 for premenopausal and 34 for postmenopausal breast cancer.

Menopausal age unspecified

Most of the studies showed increased risk. Meta-analysis for the Second Expert Report showed a 9 per cent increased risk per 5cm of height for cohort studies and a 3 per cent increased risk per 5cm of height for case-control studies (Page 233 Second Expert Report).

Premenopause

Most of the studies showed increased risk. Meta-analysis for the Second Expert Report showed a 9 per cent increased risk per 5cm of height for cohort studies and a 4 per cent increased risk per 5cm for case-control studies (Page 235 Second Expert Report). An updated meta-analysis of cohort studies also showed a 9 per increased risk per 5cm of height (Figure Ht1 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of four cohort studies with 723 cases of premenopausal breast cancer followed up for up to 11 years showed a non-significant increased risk with greater adult attained height.[51]

Postmenopause

Nearly all the cohort studies and most case-control studies showed increased risk, with no studies showing statistically significant contrary results. Meta-analyses for the Second Expert Report showed an 11 per cent increased risk per 5cm of height for cohort studies and a 2 per cent increased risk per 5cm for case-control studies (Page 234 Second Expert Report). An updated meta-analysis showed a 10 per increased risk per 5cm of height (Figure Ht4 2008 Continuous Update Project Breast Cancer SLR. A pooled analysis of seven cohort studies with

3208 cases of postmenopausal breast cancer followed up for up to 11 years showed a significantly significant 7 per cent increased risk per 5cm of height.[51]

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 and box 2.4 of the Second Expert Report. Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

Premenopause: There are fewer data for premenopausal than for postmenopausal breast cancer. The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. The epidemiological evidence is generally consistent, with a dose-response relationship and evidence for plausible mechanisms. The conclusion reached for the Second Expert Report remains unchanged. The factors that lead to greater adult height, or its consequences, are probably a cause of premenopausal breast cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant epidemiological evidence, which is generally consistent, with a clear dose-response relationship and evidence for plausible mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

6.6 Abdominal fatness (postmenopause)

(Also see sections 8.2.1 Waist Circumference and 8.2.3. and Waist to hip ratio of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 3 new cohort studies[42, 47, 48] and 1 recent publication from a previously included cohort study[58] that investigated waist circumference and 3 cohort studies[42, 47, 48] and 2 recent publications from previously included cohort studies[28, 59] that investigated waist to hip ratio. In total 9 cohort studies investigated waist circumference and 13 waist to hip ratio. The Second Expert Report included 3 case-control studies that investigated waist circumference and 8 that investigated waist to hip ratio.

All of the waist circumference studies and most of those on waist to hip ratio showed increased risk with increased measures of abdominal fatness. Meta-analysis of cohort studies for the Second Expert Report showed a 5 per cent increased risk per 8 cm in waist circumference (Page 226 Second Expert Report). The updated meta-analyses were stratified by whether the study adjusted for BMI. Studies that did not adjust for BMI showed a 7 per cent increased risk per 8cm in waist circumference and those that did showed a 4 per cent increased risk (Figures W5 and W6 2008 Continuous Update Project Breast Cancer SLR).

Meta-analysis of cohort studies for the Second Expert Report showed a 19 per cent increased risk per 0.1 increment in waist to hip ratio (Page 226 Second Expert Report). The updated meta-analyses were stratified by whether the study adjusted for BMI. Studies that did not adjust for BMI showed a 9 per cent increased risk per 0.1 increment in waist to hip ratio and those that did showed a non-significant increased risk (Figures WHR6 and WHR7 2008 Continuous Update Project Breast Cancer SLR).

The general mechanisms through which abdominal fatness could plausibly cause cancer are outlined in chapter 6.1.3 9 and box 2.4 of the Second Expert Report. The hormonal and other biological effects of being overweight or obese are outlined in chapter 8 of the Second Expert Report. Many of these, such as increased levels of circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is a substantial amount of epidemiological evidence but some inconsistency. There is robust evidence for mechanisms that operate in humans. The conclusion reached for the Second Expert Report remains unchanged. Abdominal fatness is a probable cause of postmenopausal breast cancer.

6.7 Adult weight gain (postmenopause)

(Also see section 8.1.6 Weight Change of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 3 new cohort studies[42, 47, 48] and 1 recent publication from a previously included cohort study[60] that investigated adult weight change and postmenopausal breast cancer. In total 10 cohort studies investigated adult weight change. The Second Expert Report included 17 case-control studies that investigated adult weight change. Nearly all the studies showed increased risk with increased weight gain in adulthood. Meta-analyses for the Second Expert Report showed a 3 per cent increased risk per 5kg gained for the cohort studies and a 5 per cent increased risk per 5kg for case-control studies (Page 227 Second Expert Report). Heterogeneity may be explained by failure to separate postmenopausal women taking hormone replacement therapy.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see chapter 2.7.1.3 Second Expert Report). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers.

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is ample, consistent epidemiological evidence and a dose-response relationship was apparent. The conclusion reached for the Second Expert Report remains unchanged. Adult weight gain is a probable cause of postmenopausal breast cancer.

6.8 Greater birth weight (premenopause)

(Also see section 8.4.1 Birthweight of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 1 new cohort study[61] that investigated birth weight and premenopausal breast cancer. In total 6 cohort and 4 case-control studies investigated birth weight. All cohort studies and most case-control studies showed increased risk with greater birth weight. Meta-analysis of cohort studies for the Second Expert Report showed an 8 per cent increased risk per kg (Page 238 Second Expert Report).

The general mechanisms through which the factors that lead to greater birth weight, or its consequences, could plausibly influence cancer risk are outline in chapter 6.2.11. of the Second Expert Report many of these, such as long-term programming of hormonal systems, could plausibly increase cancer risk. Greater birth weight raises circulating maternal oestrogen levels and may increase insulin-like growth factor (IGF)-1 activity; low birth weight raises fetal and maternal levels of IGF-1 binding protein. The action of both oestrogens and IGF-1 are thought to be important in fetal growth and mammary gland development, and play a central, synergistic role in the initiation and promotion of breast cancer.[62] Animal experiments also provide evidence that exposure to oestrogens during fetal and early postnatal development can increase the risk of mammary cancers.[63]

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is general consistency amongst the relatively few epidemiological studies, with some evidence for a dose-response relationship. The mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. The factors that lead to greater birth weight, or its consequences, are probably a cause of premenopausal breast cancer.

6.9 Total fat (postmenopause)

(Also see section 5.2 Total Fat of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 1 new cohort study[64] and 1 recent publication from a previously included cohort study[65] that investigated total fat intake and 1 new cohort study[66] and 1 recent publication from a previously included cohort study[67] that investigated energy from fat and postmenopausal breast cancer. In total 9 cohort studies investigated total fat intake and 5 cohort studies investigated energy from fat and postmenopausal breast cancer. The Second Expert Report included 16 case-control studies that investigated total fat intake and postmenopausal breast cancer. For total fat most studies showed increased risk with increased intake. Meta-analyses for the Second Expert Report showed a non-significant increased risk for cohort studies and an 11 per cent increased risk per 20g/day for case-control studies (Page 138 Second Expert Report). A pooled analysis of cohort studies of more than 7300 cases of breast cancer showed an overall non-significant decreased risk with increased fat intake. Menopausal status did not significantly alter the result.[68] For energy from fat

most cohort studies reported decreased risk with increasing per cent energy from fat and one reported a statistically significant increased risk.

The Women's Health Initiative Dietary Modification Randomised Controlled Trial with 655 cases of postmenopausal breast cancer reported a relative risk of 0.91 (0.83-1.01) for intervention and comparison group after 8.1 years.[69] Adjusting for change in body weight had no effect on the relative risk. The trial was designed to reduce fat intake to 20% and increase servings of vegetables and fruit to 5 per day and increase servings of grains to at least 6 per day. However for women with at least 36.8% energy from fat at baseline a decrease was observed for intervention compared with control (RR- 0.78 (0.64-0.95)).

Higher endogenous oestrogen levels after menopause are a known cause of breast cancer.[53, 70] Dietary fat may also increase endogenous oestrogen production.[71]

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. Evidence from prospective epidemiological studies of different types on the whole shows inconsistent effects, while case-control studies show a significant positive association. Mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. Overall, there is limited evidence suggesting that consumption of total fat is a cause of postmenopausal breast cancer.

6.10 Other exposures

For pre- and postmenopausal breast cancer, other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. The list of exposures is shown in the matrices under limited – no conclusion. Additional meta-analyses of cohort studies on dietary fibre and highest versus lowest category forest plots for total, red and processed meat, fish, dietary folate and energy were also conducted as part of the Continuous Update Project (See 2008 Continuous Update Project Breast Cancer SLR for details).

There is considerable speculation around a biologically plausible interaction of soy and soya products with breast cancer development, due to their high phytoestrogen content. Data on pulses (legumes) were sparse and inconsistent.

A meta-analysis of 3 cohort and 6 case-control studies showed a statistically significant 25 per cent lower risk of breast cancer at any age for highest versus lowest intake of soy products. [72]

A meta-analysis of 6 cohort and 12 case-control studies reported a statistically significant 14 per cent lower risk of breast cancer at any age for highest versus lowest consumption of soy protein (estimated from intake of soy food and dietary isoflavones). [73] Another meta-analysis reported a statistically significant 12 per cent lower risk of breast cancer at any age for highest versus lowest intake of isoflavones.[74] In a subgroup analysis the association was statistically significant for Asian populations (29 per cent lower risk) but not for Western populations. [74] These meta-analyses are limited by the difficulty in the standardisation of

measure of soy intake. The quantity and type of soy consumed varied greatly across the studies, such that the contrasts in intake levels for the reported risk estimates differed widely. Although results of these meta-analyses suggest that soy intake is associated with a modest reduction in breast cancer risk, heterogeneity across studies limits the ability to interpret the findings.

7. Comparison with the Second Expert Report

Overall the evidence from the additional cohort studies identified in the Continuous Update Project was consistent with those reviewed as part of the Second Expert Report. Much of the new evidence related to body fatness, abdominal fatness and weight gain; there were also new studies reporting on alcohol consumption.

8. Conclusions

Since the new evidence that was found as part of the Continuous Update Project is consistent with the evidence presented in the Second Expert Report the conclusions are unchanged.

The Continuous Update Project Panel concludes:

The evidence that lactation protects against breast cancer at all ages thereafter is convincing. Physical activity probably protects against postmenopausal breast cancer, and there is limited evidence suggesting that it protects against premenopausal breast cancer. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater attained adult height or its consequences are a cause of postmenopausal breast cancer is convincing; these are probably a cause of premenopausal breast cancer.

The factors that lead to greater birth weight or its consequences are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably a cause of this cancer. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

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Appendix 1 Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

This box lists the criteria finally agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

Convincing

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

Probable

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

All the following were generally required:

- Evidence from at least two independent cohort studies, or at least five case control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Evidence for biological plausibility.

Limited — suggestive

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The

evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.

All the following were generally required:

- Evidence from at least two independent cohort studies or at least five case control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

Limited — no conclusion

Evidence is so limited that no firm conclusion can be made. This category represents an entry level, and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited — no conclusion' for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.

When an exposure is graded 'limited — no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the Diet and Cancer Report website (www.dietandcancerreport.org). However, such evidence is usually not included in the summaries.

Substantial effect on risk unlikely

Evidence is strong enough to support a judgement that a particular food, nutrition, or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high versus low exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error,

including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias.
- Absence of a demonstrable biological gradient ('dose response').
- Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, an insufficient range of exposure in the study population, and inadequate statistical power. Defects in these and other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or in humans that a specific mechanism exists, or that typical exposures can lead to cancer outcomes, argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful, and could overlap with judgements of 'limited — suggestive' or 'limited — no conclusion'.

Special upgrading factors

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. So an exposure that might be deemed a 'limited — suggestive' causal factor in the absence, say, of a biological gradient, might be upgraded to 'probable' in its presence. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

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Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition

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Key words: alcohol consumption, breast cancer, prospective study

Abbreviations: BC: breast cancer; BMI: body mass index;; CI: confidence interval; EPIC: European prospective investigation into cancer and nutrition; ER: estrogen receptor; FFQ: food-frequency questionnaire; FFTP: first full-term pregnancy; HER2: human epidermal growth factor receptor; HR: hazard ratio; PR: progesterone receptor

Additional Supporting Information may be found in the online version of this article.

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Alcohol intake has been associated to breast cancer in pre and postmenopausal women; however results are inconclusive regarding tumor hormonal receptor status, and potential modifying factors like age at start drinking. Therefore, we investigated the relation between alcohol intake and the risk of breast cancer using prospective observational data from the European Prospective Investigation into Cancer and Nutrition (EPIC). Up to 334,850 women, aged 35–70 years at baseline, were recruited in ten European countries and followed up an average of 11 years. Alcohol intake at baseline and average lifetime alcohol intake were calculated from country-specific dietary and lifestyle questionnaires. The study outcomes were the Hazard ratios (HR) of developing breast cancer according to hormonal receptor status. During 3,670,439 person-years, 11,576 incident breast cancer cases were diagnosed. Alcohol intake was significantly related to breast cancer risk, for each 10 g/day increase in alcohol intake the HR increased by 4.2% (95% CI: 2.7–5.8%). Taking 0 to 5 g/day as reference, alcohol intake of >5 to 15 g/day was related to a 5.9% increase in breast cancer risk (95% CI: 1–11%). Significant increasing trends were observed between alcohol intake and ER+/PR+, ER−/PR−, HER2− and ER−/PR−HER2− tumors. Breast cancer risk was stronger among women who started drinking prior to first full-time pregnancy. Overall, our results confirm the association between alcohol intake and both hormone receptor positive and hormone receptor negative breast tumors, suggesting that timing of exposure to alcohol drinking may affect the risk. Therefore, women should be advised to control their alcohol consumption.

Epidemiology

What's new?

Although it is now established that alcohol consumption increases breast cancer risk, many questions remain. Using a prospective study design with 11,576 incident breast cancer cases across 10 European countries, the authors confirmed the increased risk of alcohol on breast cancer development. They further show that women who started drinking before their first full-term pregnancy have a higher risk than women who started afterwards. These effects were observed in hormone-receptor positive and –negative tumors pointing to non-hormonal pathways that need to be further investigated.

A consistent association has been observed between alcohol intake and breast cancer (BC) among both pre and postmenopausal women,[1] with a linear dose-response increase ranging from 2%[2] to 12%[3] for each additional drink per day (equivalent to about 10 g/day). While the association is firmly established, some questions such as the association with specific tumor subtypes, the impact of the age at start drinking and a potential window of susceptibility, remain unanswered. Mechanistic evidences show that ethanol stimulates both cell proliferation and estrogen receptor (ER) signaling in the mammary gland.[4–6] Most epidemiological studies report an impact of ethanol on ER+ tumors.[7] However a recent meta-analysis showed an increased risk in both hormone receptor positive and negative tumors.[8] The consumption of alcoholic beverages may interact with other BC risk factors such as hormonal status or first full-term pregnancy (FFTP),[9,10]and thus differentially modulate breast cancer risk over a woman's lifetime.[11] Recent studies report that low to moderate alcohol intake between menarche and first pregnancy is associated with BC risk.[12] It is, therefore, important to evaluate the association of alcohol intake and BC phenotypes in light of a potential modulating effect of age at start drinking.

Material and Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort consists of approximately 370,000 women and 150,000 men, aged 35–69, recruited between 1992 and 1998 in 23 research centers across 10 Western European countries, Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), Greece, Italy (Florence, Varese, Ragusa, Turin, and Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, and San Sebastian), Sweden (Malmö and Umeå), the Netherlands (Bilthoven and Utrecht) and the United Kingdom (Cambridge and Oxford). The design and methodology has been published elsewhere.[13] Eligible men and women were invited to participate; those who accepted gave informed consent and compiled questionnaires on diet, lifestyle, and medical history. EPIC recruited 367,993 women, aged 35–70 years. Women with prevalent cancers at any site at recruitment ($n = 19,853$) or with missing diagnosis or censoring date ($n = 2,892$) were excluded. A total of 3,339 subjects with missing dietary or lifestyle information, and 6,753 women in the top and bottom 1% of the ratio of energy intake to estimated energy requirement, calculated from age, sex, body weight and height, were excluded from the analysis. In addition, 217 nonfirst breast cancer cases were excluded. Thus, the analysis was performed in 334,850 EPIC women with complete exposure information. Within this group, 11,576 women with invasive breast cancer (including 1,227 carcinoma *in situ*) were identified after a median follow-up of 11.0 years. Information on lifetime alcohol consumption was missing for Sweden, Norway, Naples and Bilthoven, 24.1% were then excluded from the subanalyses on lifetime alcohol intake. The study was approved by IARC ethical committee and the local ethical committees of the participating centers.

Dietary assessment, lifestyle and alcohol consumption

Dietary and lifestyle questionnaires were completed by participants at enrolment when anthropometric measurements were taken.[13] Past-year physical activity (PA) in occupational and recreational domains was assessed at baseline with a self-administered questionnaire. For occupational activity, both employment status as well as the level of physical activity done during work was recorded as: nonworker, sedentary, standing, manual, heavy manual and unknown (for which duration and frequencies were not recorded). Recreational time physical activity included walking, cycling and sport activities. The duration and frequency of recreational activity were multiplied by the intensity assigned by metabolic equivalent values (METs) for the different activities. A total PA index, the "Cambridge PA Index" was estimated by crosstabulating occupational with recreational PA. This index is based on occupational, cycling and sport activities.

Information on alcohol use at the time of enrolment into the study was based on a dietary assessment of usual consumption of alcoholic beverages and types of alcoholic beverage (*i.e.*, wine, beer, spirits and liquors) during the past 12 months. In each country, intake was calculated based on the estimated average glass volume and ethanol content for each type of alcoholic beverage, using information collected in highly standardized 24-hr dietary recalls from a subset of the cohort.[14] Information on past alcohol consumption (available for 75.9% of participants) was assessed as glasses of different beverages consumed per week at 20, 30, 40 and 50 years of age. Average lifetime alcohol intake was determined as a weighted average of intake at different ages, with weights equal to the time of individual exposure to alcohol at different ages. To determine which women had started drinking prior to FFTP, we used information on alcohol consumption at different ages and the age of FFTP reported by the women in the questionnaire.

Anthropometric measurements

Weight and height were measured at baseline, while the subjects were not wearing shoes, to the nearest 0.1 kg, or to the nearest 0.1, 0.5 or 1.0 cm, depending on the center.[15] In France, Norway and Oxford, height and weight were self-reported on a questionnaire. The procedures used to account for procedural differences between centers in the collection of anthropometric measurements are described elsewhere.[16]

Perspective ascertainment of breast cancer cases, coding of receptor status and determination of menopausal status

Incident BC cases were identified through population cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom) or by active follow-up (France, Germany, Naples and Greece). The active follow-up procedure used a combination of methods, including health insurance records, cancer and pathology registries and contacts

with participants and their next-of-kin. Subjects were followed up from study entry and until cancer diagnosis (except for nonmelanoma skin cancer cases), death and emigration or until the end of the follow-up period, whichever occurred first. The end of follow-up period was: December 2004 (Asturias), December 2006 (Florence, Varese, Ragusa, Granada and San Sebastian), December 2007 (Murcia, Navarra, Oxford, Bilthoven, Utrecht and Denmark), June 2008 (Cambridge), December 2008 (Turin, Malmo, Umea and Norway). For study centers with active follow-up, the last follow-up contact was: December 2006 for France, December 2009 for Greece, June 2010 for Heidelberg, December 2008 for Potsdam and December 2006 for Naples. Cancer incidence data were classified according to the International Classification of Diseases for Oncology, Second Revision (ICDO-2).

Information on tumor receptor status, on the available laboratory methods and on quantification descriptions used to determine receptor status, were collected by 20 centers. Information on ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) was provided by each center based on pathology reports. To standardize the quantification of receptor status among the EPIC centers, the following criteria for a positive receptor status were used: $\geq$10% cells stained, any "plus-system" description, $\geq$20 fmol/mg, an Allred score of $\geq$3, an IRS $\geq$2 or an H-score $\geq$10.[17–21]

Women were considered as premenopausal when reporting regular menses over the past 12 months, or when aged <46 years at recruitment. Women were considered as postmenopausal when not reporting any menses over the past 12 months, or having received bilateral ovariectomy. Women with missing or incomplete questionnaire data or with previous hysterectomy, were considered postmenopausal only if older than 55 years of age. Women were considered with unknown menopausal status when aged between 46 and 55 years and had missing or incomplete questionnaire data, or reported previous hysterectomy (without ovariectomy).[22,23]

Statistical analysis

Cox proportional hazards regression models were used to quantify the association between alcohol consumption and breast cancer risk. Age was the primary time variable and the Breslow method was adopted for handling ties.[24] Time at entry was age at recruitment; time at exit was age at cancer diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. Models were stratified by center to control for differences in questionnaire design, follow-up procedures and other center effects. Further stratification by age at recruitment (1-year categories) was used. Systematic adjustments were made for menopausal status (dichotomized as postmenopausal or women that underwent an ovariectomy *vs.* other), weight and height (all continuous), smoking (never, former, and current), educational attainment (five categories of schooling) as a proxy variable for socioeconomic status, physical activity (inactive, moderately inactive, moderately active, active). In addition, the following variables were included in the models: age at menarche ($\leq$12, 12–14, >14 years), age at birth of first child (nulliparous, $\leq$21, 21–30, >30 years), and age at menopause ($\leq$50, >50 years), ever use of contraceptive pill and ever use of replacement hormones, energy intake without alcohol consumption and adjustment for interaction "menopause, weight."

Alcohol consumption was modeled as both continuous and categorical variable (none, 0.1–5, 5.1–15, 15.1–30, >30 g/day). Both baseline consumption and lifetime consumption were studied. Correlation between both estimations was high ($r = 0.80$). *P*-trend values were obtained by modeling a score variable (from 1 to 5) category-specific level of alcohol at baseline. In addition, the shape of the dose-response curve between alcohol consumption and breast cancer risk was evaluated with fractional polynomials of order two,[25] using 3 g/day as reference value and after exclusion of former consumers at baseline. Nonlinearity was tested comparing the difference in log-likelihood of a model with fractional polynomials with a model with a linear term only to a chi-square distribution with three degrees of freedom.[25] For all models, the proportional hazards assumption was satisfied, evaluated *via* inclusion into the disease model of interaction terms between exposure and attained age (data not shown). Statistical heterogeneity of associations across countries or receptor status, was based on a χ^2 statistics, computed comparing country-specific coefficients to an overall coefficient. Stratified analyses were conducted according to the time at start drinking (prior of after FFTP) and interaction term was tested using alcohol intake as continuous variable in multivariate models. Models were run with the exclusion of the first 2 years of follow-up, but the results did not differ from those including the entire cohort (data not shown).

Statistical tests were two sided, and *p*-values <0.05 were considered significant. All analyses were performed using SAS version 9.2 (SAS Institute, 1999) and STATA (Stata Statistical Software: Release 12 (2011) StataCorp.,College Station, TX: StataCorp LP).

Results

During an average of 11.0 years of follow-up (3,670,43940 person-years) of 334,850 study participants, the EPIC study documented 11,576 incident BC cases (e-Table 1). The overall percentage of women drinking over 15 g/day at baseline was 16.3% (e-Table 1).

The mean age at recruitment was 50.8 years, and the mean age at BC diagnosis was 59.4 years. Table 1 presents the baseline alcohol intake according to the distribution of major baseline demographic and lifestyle characteristics. At baseline, 35.2% of women were premenopausal and 43.1% postmenopausal (the menopausal status of 18.8% of women was not defined, and 2.9% reported bilateral ovariectomy; Table 1). No drinkers at baseline were less likely to ever have used exogenous hormones and less likely to have ever smoked, were more moderately active and attained less education at baseline than drinkers at baseline (Table 1).

Table 1. Demographic and lifestyle characteristics according to breast cancer status and alcohol intake at baseline

Demographic and lifestyle characteristics[1]	Breast cancer cases	Noncases	Average daily alcohol intake (g/day)				
			0	0.1–5	5.1–15	15.1–30	>30
Participants (*N*)	11,576	323,274	54,907	135,599	89,694	35,460	19,190
Age at recruitment (years) (mean, SD)	52.2 (8.8)	50.8 (10.2)	52.2 (9.0)	50.9 (9.8)	50.1 (9.5)	50.2 (9.0)	50.2 (9.0)
Breast cancer cases (*N*, %)	11,576	—	1,626 (2.96)	4,280 (3.16)	3,261 (3.64)	1,475 (4.16)	934 (4.87)
Receptor status (*N*, %)							
ER+/PR+	3,653 (31.6)	—	527 (0.98)	1,367 (1.03)	970 (1.11)	472 (1.37)	317 (1.71)
ER+/PR−	1,133 (9.8)	—	177 (0.33)	404 (0.31)	303 (0.35)	162 (0.47)	87 (0.42)
ER−/PR−	1,050 (9.1)	—	131 (0.25)	441 (0.33)	252 (0.29)	132 (0.39)	94 (0.51)
HER−	1,764 (75.6)	—	246 (0.46)	662 (0.50)	457 (0.53)	238 (0.70)	161 (0.87)
HER+	570 (24.4)	—	88 (0.16)	231 (0.18)	132 (0.15)	81 (0.24)	38 (0.21)
ER−/PR−/HER−	226 (2.0)	—	25 (0.05)	84 (0.06)	62 (0.07)	29 (0.09)	26 (0.14)
Menopausal status (%)							
Premenopausal	24.4	35.2	31.4	37.2	35.5	32.5	29.1
Perimenopausal	22.0	18.8	17.3	18.8	19.2	20.3	20.6
Postmenopausal	50.7	43.1	47.3	41.4	42.7	44.5	47.1
Surgical postmenopausal	2.8	2.9	4.0	2.6	2.6	2.7	3.2
Reproductive factors							
Age at menarche (years) (mean, SD)	12.95 (1.51)	13.01 (1.75)	13.03 (1.57)	12.98 (1.68)	13.01 (1.65)	13.02 (1.55)	12.99 (1.56)
Age at menopause (years) (mean, SD)[2]	49.52 (4.72)	49.03 (5.85)	48.80 (4.96)	49.09 (5.29)	49.20 (5.27)	49.17 (4.89)	49.07 (4.91)
Nulliparous (%)	13.7	15.2	10.8	14.5	17.3	17.2	18.7
N of full-term pregnancies (mean, SD, range)	1.90 (1.17) (0–9)	1.99 (1.37) (0–17)	2.05 (1.21) (0–17)	2.01 (1.30) (0–14)	1.94 (1.28) (0–13)	1.90 (1.20) (0–12)	1.86 (1.20) (0–11)
Ever breastfed (%)	71.7	72.2	75.3	73.4	71.1	68.8	67.1
Exogenous hormone use (%)							
Ever-used HRT[2]	54.1	42.2	28.6	42.4	48.0	48.8	50.9
Ever-used OC	58.8	58.7	40.7	58.5	65.2	65.0	68.9
Duration of OC use	6.56 (6.95)	6.48 (9.15)	6.11 (7.08)	6.32 (8.18)	6.66 (8.06)	6.82 (7.27)	7.23 (7.21)
Anthropometric factors							
Height (cm) (mean, SD)	161.62 (5.89)	161.08 (6.82)	160.48 (6.06)	160.94 (6.58)	161.42 (6.39)	161.70 (6.02)	162.02 (6.03)
Weight (kg) (mean, SD)	66.20 (11.22)	65.70 (13.01)	66.60 (11.57)	65.96 (12.56)	64.99 (12.19)	64.88 (11.49)	65.38 (11.51)

Table 1. Demographic and lifestyle characteristics according to breast cancer status and alcohol intake at baseline (Continued)

Demographic and lifestyle characteristics[1]	Breast cancer cases	Noncases	Average daily alcohol intake (g/day)				
			0	0.1–5	5.1–15	15.1–30	>30
Waist-to-hip ratio (mean, SD)	0.80 (0.06)	0.80 (0.08)	0.80 (0.07)	0.80 (0.07)	0.79 (0.07)	0.80 (0.07)	0.80 (0.07)
BMI (mean, SD)[3]	25.40 (4.08)	25.37 (4.73)	25.91 (4.20)	25.50 (4.56)	25.00 (4.42)	24.87 (4.17)	24.97 (4.18)
Obese (BMI $\geq$30 kg/m^2) (%)	11.4	12.7	22.3	13.1	8.9	7.8	8.1
Smoking status (%)							
Never smoker	56.0	57.0	67.2	58.8	54.8	49.5	39.2
Former smoker	25.0	23.0	14.8	22.3	26.3	27.5	29.3
Current smoker	19.0	20.0	18.1	19.0	18.9	23.0	31.5
Total physical activity (%)							
Inactive	17.8	16.0	9.0	15.5	20.0	20.1	22.1
Moderately inactive	41.3	37.1	32.3	37.3	39.0	39.7	41.8
Moderately active	34.4	39.1	51.4	38.8	33.6	33.2	29.5
Active	6.6	7.8	7.3	8.4	7.4	7.0	6.6
Highest education level (%)							
None or primary school	26.1	29.7	52.5	28.8	22.1	21.8	17.4
Secondary/technical/ professional school	48.6	46.8	34.7	50.1	49.2	47.1	49.5
University	25.3	23.5	12.9	21.2	28.7	31.1	33.1
Dietary intake (mean, SD)							
Total energy intake (kcal/day)	1,976 (512)	1962 (594)	1,868 (522)	1,926 (567)	1,993 (550)	2,086 (519)	2206 (520)
Total energy without alcohol (kcal/day)	1,918 (505)	1909 (586)	1,868 (521)	1,913 (566)	1,928 (549)	1,939 (518)	1902 (519)
Total dietary fiber (g/day)	22.1 (7.1)	22.1 (8.2)	22.1 (7.3)	22.4 (8.0)	22.2 (7.7)	21.6 (7.3)	20.6 (7.3)

Note: Unknown values were excluded from the calculations. HRT: hormone replacement therapy; OC: oral contraceptives; SD: standard deviation; BMI: body mass index; All p values <0.0001, except for age at menarche (not significant); Trend test for continuous variables; Cochran–Armitage test for trend for categorical variables and global χ^2 test.
Missing data in the total cohort were: 3.2% for age at menarche; 4.6% for parity; 2.5% for oral contraceptive; 2.3% for smoking status; 15.3% for physical activity; 7.7% for diabetes; 14.4% for hypertension; 28.4% for waist-to-hip ratio; 3.9% for education level; in postmenopausal women: 5.3% for HRT and 24.3% for age at menopause.
[1]Continuous variables are presented as means and standard deviations (SD), adjusted by age at recruitment and center (except age, which is adjusted by center only).
[2]Among postmenopausal women only.
[3]Weight (kg)/height (m)^2.

Alcohol intake showed a significant positive dose-response relation with BC ($p < 0.0001$, Table 2). BC hazard ratio (HR) was increased by 6% (95% CI: 1–11%), 12% (95% CI: 6–19%) and 25% (95% CI: 17–35%) for the consumption of 5–15 g/day, 15–30 g/day and >30 g/day, respectively, compared to the 0.1–5 g/day category of intake. For each additional 10 g/day the HR increased by 4% (95% CI: 3–6%). Figure 1 shows the relation between alcohol intake and BC risk, fractional polynomial of order 2 using 3 g/day as reference. A statistically significant relation was observed ($p < 0.0001$), while the test for nonlinearity was compatible with a linear trend ($p = 0.100$).

When the associations were evaluated according to hormone receptor status, for each additional 10 g/day the HR significantly increased by 4% (95% CI: 1–6%) in ER+/PR+, by 5% (95% CI: 0–10%) in ER−/PR−, by 5% (95% CI: 2–9%) in HER2− and by 12% (95% CI: 3–23%) in ER−/PR−/HER2− breast tumors (Table 2). Test for heterogeneity between alcohol consumption and hormone receptor status was not significant ($p = 0.26$). No significant association was observed for ER+/PR−, ER−/PR+ and HER2+. When using lifetime alcohol intake slightly lower estimates were observed (see eTable2). Similar results were observed for pre and postmenopausal women, although, given the smaller sample size among premenopausal women, statistically significance was reached only in the overall analysis. There was no heterogeneity in results between pre and postmenopausal women (p interaction = 0.48). No interaction was observed with body mass index (BMI) or use of exogenous hormones either. Since statistical adjustment for smoking can be difficult, analyses in nonsmokers at baseline were carried out and results remained virtually similar (data not shown).

Age at start drinking according to FFTP, was positively related to BC risk among women who start drinking prior to FFTP. Stronger associations were observed for ER−, PR−, ER−/PR− and ER−/PR−/HER2− tumors (Table 3). In a multivariable model, an increase of 10 g of alcohol/day was related to an 8% (95% CI: 2–14%) increased risk of ER− tumors in women who start drinking prior to FFTP, while no association could be detected among women who start drinking after FFTP (p for interaction = 0.047), and a 9% (95% CI: 2–16%) increased risk of ER−/PR− tumors in women who start drinking prior to FFTP (p for interaction = 0.10). When using lifetime alcohol intake slightly lower estimates were observed (see eTable3). We were not able to evaluate the amount of alcohol consumed prior to FFTP.

BC hazard ratios, with data stratified according to the median period between menarche and FFTP (13 years) among women who start drinking prior to FFTP, was of 5.6% (95% CI: 2.6–8.8%) among women with longer median period and of 2.6% (95% CI: 1.0–6.2%) among their counterpart. These data suggest that a longer time between menarche and FFTP may modulate BC risk among women who start drinking prior to FFTP. However, the test for interaction was not significant ($p = 0.23$) (data not shown).

Discussion

In this prospective study of 334,850 women and 11,576 incident BC cases, an increased intake of 10 g of alcohol/day was related to a 4.2% increased BC risk (95% CI: 2.7–5.8%). This was observed for both ER+/PR+ and ER−/PR− tumor subtypes with the largest risk observed for triple negative tumors (ER−/PR−/HER2−). No interaction was observed with BMI and use of hormones. Women who started drinking before their FFTP appeared to be at higher risk for BC than women who started drinking after their FFTP.

Most studies published to date have reported an increased BC risk with increasing alcohol intake.[1] A previous analysis within the EPIC cohort on a smaller number of BC cases ($n = 4{,}285$), reported a 3% increase in BC incidence for each additional 10 g/day of alcohol.[26] Our results, based on [mt]11,000 incident BC cases, confirm our previous results and suggest a slightly stronger association. We did not observe strong differences in estimates across tumor receptor status (triple negative tumors showed the strongest risk, however, the sample size in this category was small). Although most of prior studies have reported a higher risk for ER+ and/or PR+ tumors compared to ER− and/or PR− tumors in particular, for the highest *versus* the lowest alcohol intake group,[9,27–33] an increased risk for hormone receptor negative tumors was also reported.[8,34,35] This inconsistency of results across studies might be partially due to the smaller number of BC cases with negative hormone receptor status. The very large number of both hormone receptor positive and hormone receptor negative tumors in our study increased our power on the association. Nonhormonal pathways such as DNA damage are likely to be involved in the incidence of receptor negative tumors.[8] The effect of alcohol appears linear, suggesting that there is no safe level of intake for BC risk.

A limited number of studies have investigated the presence of a window of susceptibility to alcohol carcinogenesis in the breast. Some epidemiological studies suggest that drinking alcohol during adolescence or early adulthood has a strong impact on BC risk.[36] Results from the Nurses' Health Study II show that low to moderate alcohol intake during adolescence and early adulthood is dose-dependently associated with an increased risk of proliferative benign breast disease, which may lead to invasive BC later in life.[37] More recent results support the effect of drinking alcohol between menarche and FFTP on BC risk (RR = 1.11 per 10 g/day intake; 95% CI: 1.00–1.23) and on proliferative benign breast disease (RR = 1.16 per 10 g/day intake; 95% CI: 1–1.02).[11] In addition, the association between drinking before FFTP and development of breast neoplasia appeared to be stronger with longer menarche to first pregnancy intervals. These results are consistent with the hypothesis that alcohol carcinogens may preferentially act during mammary development.[38] We observed a stronger effect of alcohol intake prior to FFTP, with a significant interaction for receptor negative tumors. Our findings suggest that starting drinking before FFTP might be a more sensitive period, even if we cannot exclude the

Table 2. Breast cancer risk by hormonal subtypes according to alcohol consumption at baseline

N cases/ person-years	Average daily alcohol intake at baseline (g/day)					*p* values (trend)[2]	HR (95% CI) per 10 g/day	*p*-value[3]
	0[1]	0.1–5	5.1–15	15.1–30	>30			
All cases	1,626/605,217	4,280/1,488,055	3,261/983,711	1,475/387,280	934/206,177		11,576/3,670,440	
	1.04 (0.98–1.10)	1.00 (ref)	1.06 (1.01–1.11)	1.12 (1.06–1.19)	1.25 (1.17–1.35)	<.001	1.04 (1.03–1.06)	<.001
ER+/PR+	527/598,625	1,367/1,470,607	970/969,575	472/381,199	317/202,569		3,653/3,622,575	
	1.06 (0.95–1.18)	1.00 (ref)	1.09 (1.00–1.18)	1.11 (0.99–1.23)	1.30 (1.15–1.48)	0.001	1.04 (1.01–1.06)	0.003
ER+/PR−	177/596,367	404/1,464,086	303/965,046	162/379,089	87/200,949		1,133/3,605,537	
	1.18 (0.98–1.42)	1.00 (ref)	1.13 (0.97–1.31)	1.22 (1.01–1.47)	1.13 (0.88–1.43)	0.41	1.04 (0.99–1.09)	0.09
	27/595,288	88/1,461,768	53/963,248	35/378,194	14/200,458		217/3,598,956	
ER−/PR+	0.93 (0.59–1.45)	1.00 (ref)	1.06 (0.74–1.51)	1.37 (0.90–2.07)	1.03 (0.57–1.86)	0.26	1.05 (0.95–1.17)	0.34
ER−/PR−	131/596,019	441/1,464,103	252/964,537	132/378,867	94/200,964		1,050/3,604,490	
	0.89 (0.73–1.10)	1.00 (ref)	0.92 (0.78–1.08)	1.03 (0.84–1.26)	1.28 (1.01–1.61)	0.06	1.05 (1.00–1.10)	0.03
HER2−	246/597,134	662/1,466,665	457/966,684	238/379,950	161/201,697		1,764/3,612,130	
	1.11 (0.95–1.29)	1.00 (ref)	1.09 (0.96–1.23)	1.14 (0.98–1.34)	1.41 (1.17–1.68)	0.007	1.05 (1.02–1.09)	0.004
HER2+	88/595,882	231/1,463,254	132/964,054	81/378,655	38/200,712		570/3,602,557	
	1.14 (0.87–1.49)	1.00 (ref)	0.89 (0.72–1.12)	1.18 (0.90–1.54)	0.97 (0.68–1.39)	0.83	0.98 (0.92–1.06)	0.68
ER−/PR−/HER2−	25/595,363	84/1,461,973	62/963,514	29/378,261	26/200,594		226/3,599,705	
	1.09 (0.68–1.74)	1.00 (ref)	1.18 (0.84–1.66)	1.20 (0.77–1.86)	1.97 (1.23–3.16)	0.03	1.12 (1.03–1.23)	0.01

[1]Includes both never and former drinkers.
[2]Test for a trend in HRs by categories of alcohol intake were computed by assigning consecutive scores (1, 2, 3, 4, 5) to the categories.
[3]Test of trend for alcohol intake continuous.
Note: Stratified by center and age at recruitment (1-year interval), and adjusted for menopausal status (pre/peri *vs.*postmenopausal women), oral contraceptive use (yes/no/missing), hormone replacement therapy use (yes/no/missing), height (continuous), weight (continuous), interaction menopause and weight, smoking status (never, ex, current and missing), educational level (primary, no schooling, technical or professional or secondary, longer education, missing), physical activity (inactive, moderately active, moderately inactive, active and unknown), age at first menses (≤ 12, 13–14, 15+, missing), age at first full term pregnancy (nulliparous, ≤21, 22–30, >30, missing), age at menopause (<50, ≥50, missing) and energy intake without alcohol intake.

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possibility that the stronger association between alcohol intake and BC in women who started drinking before FFTP might be the consequence of longer duration and amount of drinking.

In our study, demographic characteristic, lifestyle and alcohol intake of women with available hormone receptor status could have differed from women with unavailable status. However, we did not observe such differences among cases with known and unknown ER status and sub analyses of these groups led to similar overall results. Similar strategies were adopted to inspect BC cases with and without available information on PR and HER2 status. In addition, a bias due to the influence of preclinical disease on alcohol intake is unlikely, given that similar results were obtained after exclusion of samples from the first 2 years of follow-up. However, we conducted multiple comparison analyses based on hormonal status and chance findings cannot be excluded.

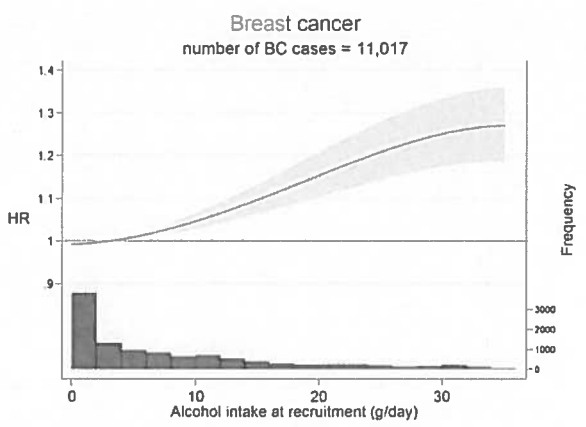

Figure 1. – Dose-response curve of BC risk with alcohol intake at recruitment. The dose-response curve is displayed up to 35 g/day, corresponding to the 99th percentile of the alcohol intake distribution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Major strengths of our study include the prospective and population based design, the large sample size, detailed information on alcohol intake at different period of life, age at start drinking and types of beverage, data on hormone receptor status, excellent follow-up and large number of cases, which provided us with good power for subgroups analyses. Information on alcohol intake was self-reported and potential misclassification may have underestimated the effect of alcohol intake. Still, assessment of alcohol intake has been shown to be reliable in the EPIC cohort[39,40] and the prospective setting of our study minimizes recall bias on age at start drinking and lifetime alcohol intake. We were unable to determine the amount of alcohol consumed before FTTP and while consumption both at baseline and over lifetime was

Table 3. Breast cancer risk among parous women with alcohol intake at baseline by age at start drinking before/after first full-term pregnancy

		Average daily alcohol intake at baseline			
	Age at start drinking	*N* cases/person-years	HR (95% CI) for 10 g/day	*p*-value	Interaction *p*-value[1]
All cases	Before FFTP	4,104/1,216,204	1.04 (1.02–1.06)	≤.001	0.14
	After FFTP	2,747/793,546	1.02 (0.99–1.05)	0.26	
ER+	Before FFTP	2,221/1,205,111	1.04 (1.01–1.07)	0.005	0.16
	After FFTP	1,460/786,197	1.02 (0.98–1.07)	0.32	
PR+	Before FFTP	1,375/1,199,890	1.04 (0.99–1.07)	0.06	0.40
	After FFTP	987/783,211	1.01 (0.96–1.07)	0.60	
ER+/PR+	Before FFTP	1,286/1,199,505	1.04 (1.00–1.08)	0.04	0.39
	After FFTP	924/782,918	1.01 (0.96–1.07)	0.65	
ER−	Before FFTP	552/1,194,218	1.08 (1.02–1.14)	0.009	0.05
	After FFTP	371/778,873	0.97 (0.88–1.06)	0.49	
PR−	Before FFTP	776/1,196,034	1.06 (1.02–1.11)	0.009	0.05
	After FFTP	545/780,237	0.98 (0.91–1.06)	0.66	
ER−/PR−	Before FFTP	383/1,193,437	1.09 (1.02–1.16)	0.01	0.10
	After FFTP	261/778,358	0.97 (0.88–1.09)	0.65	
ER−/PR−/HER2−	Before FFTP	99/1,191,822	1.17 (1.04–1.31)	0.007	0.24
	After FFTP	50/777,139	0.97 (0.75–1.24)	0.78	

[1]Age start prior to first full-term pregnancy (FFTP), was defined based on the information on 'Age at start drinking alcohol' and 'Age at first full-term pregnancy'. Results of stratified analyses by age start prior/after FFTP are displayed. Significance of interaction term was tested including in a multivariate model using alcohol as continuous variable and age start prior/after FFTP as categorical variable.
Note: Adjustments are the same as in Table 2. The statistical significance of interactions was assessed using likelihood ratio tests based on the models with and without the interaction terms formed by the product of age at start drinking alcohol before or after first pregnancy and the value of alcohol intake at recruitment.

associated with a stronger adverse effect among women who start drinking prior to FFTP than among their counterpart, our results should be interpreted with caution.

In conclusion, findings from the EPIC cohort confirm the carcinogenic effect of alcohol intake on both receptor positive and negative breast tumors. Starting to drink prior to FFTP appears to have a larger adverse effect than after FTTP. No interaction with body fatness and use of hormone was observed. Alcohol has been shown to act through the estrogen pathway, however our results suggest that nonhormonal pathways are likely to act and need to be further investigated.

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Van: Caroline van Rossum
Verzonden: maandag 24 augustus 2015 17:25
Aan: GR_RGV2015
CC: Elly Buurma; Daphne van der A
Onderwerp: reactie vijfde ronde vanuit RIVM

Beste collega's van de GR,
Hierbij de reactie vanuit het RIVM op de 5de ronde van de achtergronddocumenten RGV

Groetjes Caroline

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See http://www.voedselconsumptiepeiling.nl for information on the Dutch food consumption surveys
See http://www.rivm.nl/nevo for information on the Dutch food composition database

Reactie RIVM op concept-achtergrondrapporten RGV ronde 5

dd 24-8-2015

Alcoholhoudende dranken.

- Pag 19: r 414: fysieke activiteit is een anglicisme/Belgisch, lichamelijke activiteit (zie regel 421) is correcter Nederlands
- Pag 19, r 444: wijnconsumptie moet bierconsumptie zijn.
- Pag 29, r 690-691: de zin is incompleet.
- Pag 4, tabel 1: titel tabel 1: Gebruikelijke consumptie van … ipv Gebruikelijke inname van ..

824541

Van: Peter de Wolf
Verzonden: maandag 24 augustus 2015 20:33
Aan: GR_Bibliotheek
CC: Weggemans, R.M. (Rianne)
Onderwerp: input STIVA op uw Concept Achtergronddocument Richtlijnen goede voeding 2015 - Alcoholhoudende dranken

Geachte Gezondheidsraad,
Hierbij sturen wij u ons commentaar op uw Concept Achtergronddocument Richtlijnen goede voeding 2015 - Alcoholhoudende dranken.

Er bestaan vele discrepanties tussen het eerder geschreven ŒConcept Achtergronddocument Richtlijnen goede voeding - Alcohol[1] en dit document ŒConcept Achtergronddocument Richtlijnen goede voeding - Alcoholhoudende dranken[1]. Dit zal het formuleren van voedingsadviezen ernstig bemoeilijken.

Verder menen wij dat de beschikbare wetenschappelijke gegevens slecht bruikbaar zijn voor de gezondheidseffecten van specifieke alcoholhoudende dranken. De gegevens zijn beperkt en bovendien van slechte kwaliteit; er kleven meerdere ernstige methodologische tekortkomingen aan de gerefereerde onderzoeken. Zo is in een aantal - niet in het Concept Achtergronddocument Richtlijnen goede voeding - Alcoholhoudende dranken[1] genoemde - wetenschappelijke publicaties aangetoond dat consumenten van specifieke alcoholhoudende dranken ook verschillende leefstijlpatronen vertonen (in het bijzonder voedingspatroon), die van invloed zijn op de gevonden gezondheidseffecten. Dit maakt het lastig om gezondheidseffecten toe te schrijven aan de consumptie van één specifieke alcoholhoudende drank. Ook is het zo dat consumenten niet uitsluitend één specifieke alcoholhoudende drank drinken (en dus geen van de andere specifieke alcoholhoudende dranken).

Wij zien daarom geen meerwaarde in het werken aan Richtlijnen die verschillen per specifieke alcoholhoudende drank.

Bijgevoegd ons uitgebreide en puntsgewijze commentaar.

Met vriendelijke groet,

Peter de Wolf
Directeur

STIVA

STIVA Stichting Verantwoorde Alcoholconsumptie
Parkstraat 15-25 | 2514 JD Den Haag |
| | www.stiva.nl

Volg ons op **twitter** *@stivadewolf*

Geachte Gezondheidsraad,

Hierbij sturen wij u ons commentaar op uw Concept Achtergronddocument Richtlijnen goede voeding 2015 – Alcoholhoudende dranken.

Onze twee belangrijkste commentaren zijn:

Er bestaan vele discrepanties tussen het eerder geschreven 'Concept Achtergronddocument Richtlijnen goede voeding – Alcohol' en dit document 'Concept Achtergronddocument Richtlijnen goede voeding – Alcoholhoudende dranken'. Dit zal het formuleren van voedingsadviezen ernstig bemoeilijken.

Verder menen wij dat de beschikbare wetenschappelijke gegevens slecht bruikbaar zijn voor de gezondheidseffecten van specifieke alcoholhoudende dranken. De gegevens zijn beperkt en bovendien van slechte kwaliteit; er kleven meerdere ernstige methodologische tekortkomingen aan de gerefereerde onderzoeken. Deze tekortkomingen worden niet overwogen.

Het 'Concept Achtergronddocument Richtlijnen goede voeding 2015 - Alcohol houdende dranken acht de bewijskracht voor een groot aantal verbanden 'groot' (paragrafen 3.8 en 4). We vinden echter dat er onvoldoende wetenschappelijke basis is om drankspecifieke gezondheidseffecten te kunnen benoemen.

In meer inhoudelijk detail is ons commentaar als volgt:

1. Er bestaat een groot aantal discrepanties tussen de conclusies getrokken in de achtergronddocumenten 'alcohol' en 'alcoholhoudende dranken'. Daarom menen wij dat conclusies met betrekking tot dranktypen niet kunnen bijdragen aan een eventueel advies over de consumptie van specifieke dranktypen.

   Onduidelijk is dus hoe de verschillen tussen de uitkomsten gerapporteerd in het achtergronddocument alcoholhoudende dranken en de uitkomsten gerapporteerd in het achtergronddocument alcohol moeten worden geïnterpreteerd. Men zou immers een grote overeenkomst verwachten tussen de uitkomsten van de beide documenten. Dit is echter niet het geval; er zijn tegenstrijdigheden en veel informatie ontbreekt. De volgende tegenstrijdigheden vallen op in de conclusies van de beide documenten (zie ook Tabel 1):
   a. Het effect van alcohol op totale sterfte wordt alleen gevonden bij lagere doseringen wijn; een tegengesteld effect op totale sterfte wordt gevonden bij lagere doseringen bier en er is geen conclusie voor sterke drank
   b. Het effect van alcohol op coronaire hartziekten wordt alleen gevonden voor wijn, wordt gekenmerkt als 'onwaarschijnlijk verband' voor bier en er is geen conclusie voor sterke drank
   c. Over binge drinken is geen informatie beschikbaar
   d. Over het effect van alcohol op beroerte kan niets worden geconcludeerd voor de drie dranktypen, zowel bij lage als bij hogere consumptieniveaus

e. Over het effect van alcohol op hartfalen kan niets worden geconcludeerd voor de drie dranktypen
f. Het effect van alcohol op diabetes type II wordt alleen gevonden tot hoge doseringen bij wijn, een tegengesteld effect op diabetes type II wordt gevonden bij bier gedronken door mannen en lage consumptieniveaus van sterke drank gedronken door mannen, bij vrouwen wordt een onwaarschijnlijk verband geconcludeerd (terwijl voor alcohol juist een sterker verband lijkt te bestaan bij vrouwen)
g. Het effect van alcohol op darmkanker wordt min of meer vergelijkbaar geconcludeerd voor bier en wijn, maar niet voor sterke drank (geen conclusie)
h. Het effect van alcohol op borstkanker is niet eenduidig voor alle drie de dranktypen
i. Over het effect van alcohol op dementie kan niets worden geconcludeerd voor de drie dranktypen

Tabel 1: Overzicht conclusies met grote bewijskracht in de achtergronddocumenten 'alcohol' en 'alcoholhoudende dranken'

	Alcohol	Bier	Wijn	Sterke drank
Totale sterfte	↓ (< 30 g/d)	↑ (> 10 g/d M) ↑ (> 3 g/d V)	↑(> 20 g/d V) ↑(> 40 g/d M) ↓ (< 10 g/d V) ↓ (< 20 g/d M)	-
Coronaire hartziekten (CHZ)	↓ (> 2,5 g/d)	OV	↓ (25 g/d)	-
CHZ binge drinken	↑	-	-	-
Beroerte	↓ (< 15 g/d)	-	-	-
Beroerte	↑ (> 30 g/d)	-	-	-
Hartfalen	↓ (< 28 g/d)	-	-	-
Diabetes type II	↓ (< 24 g/d V) ↓ (< 48 g/d M)	↑ (M) OV (V)	↓ (< 60 g/d)	↑ (< 12 g/d V) OV (M)
Darmkanker	↑ (30-60 g/d)	↑(20-40 g/d)	↑(20-40 g/d)	-
Borstkanker	↑ (> 10 g/d)	Niet eenduidig	Niet eenduidig	Niet eenduidig
Dementie	↓ (< 30 g/d)	-	-	-

OV = onwaarschijnlijk verband

2. Een belangrijke methodologische kanttekening die wordt gemist is de correctie voor verstoring (confounding) in de vergelijking tussen de effecten van bier, wijn en gedistilleerde dranken. Een van de grote problemen bij het bestuderen van de effecten van de afzonderlijk alcoholhoudende dranken is dat de meeste consumenten zowel bier als wijn als gedistilleerd drinken; het komt zelden voor dat één dranktype uitsluitend wordt geconsumeerd. Veelal (ook in de studies vermeld in dit achtergronddocument) wordt een rekenkundige bewerking uitgevoerd om toch een effect van één specifieke dranksoort te kunnen afleiden. Een dergelijke bewerking houdt geen rekening met variaties in drinkpatronen (dagelijks wijn of wekelijks bier / voor of bij de maaltijd drinken) en variaties in andere factoren (geslacht; vrouwen drinken meestal wijn / leeftijd) en heeft dus tekortkomingen. Een directe vergelijking van de effecten van de drie dranktypen op de gezondheid uitsluitend door

middel van epidemiologisch onderzoek heeft dus grote methodologische nadelen en is dus niet verantwoord te maken.

3. Een tweede belangrijke methodologische kanttekening betreft de correctie van de overige leefstijlfactoren (met name dieet) bij typische bierconsumenten, wijnconsumenten en consumenten van sterke drank. Een beroemd voorbeeld is de studie door Grønbaek[1], die een duidelijk gezondheidsvoordeel liet zien voor de wijndrinker in vergelijking met de bierdrinker en de gedistilleerddrinker. Deze studie is later opnieuw geanalyseerd met een uitgebreidere correctie voor de voeding van de diverse typen drinkers[2]; door deze correctie verdwenen de verschillen tussen bier, wijn en gedistilleerd helemaal. De rol van confounding in de relatie tussen dranktype en gezondheidsuitkomst is daarna nog eens door deze groep bevestigd[3]. Het is dus zeer waarschijnlijk dat de wijndrinker een andere leefstijl (met name voeding) heeft dan de bierdrinker, waardoor de uitkomsten worden verstoord. Overigens, noemen Ferrari et al[4] dit probleem ook in hun discussie: 'Although we believe that this finding is relevant, we call for cautious interpretations of these results, as the lifestyle profile of wine and beer drinkers is profoundly different. '

4. Andere grote onderzoeken en reviews die geen effect van dranktype laten zien (op totale sterfte en coronaire hartziekten (paragrafen 3.2 en 3.3) worden niet mede overwogen in dit achtergronddocument. Deze onderzoeken zijn toegevoegd aan de referentielijst [5-9] van dit commentaar.
   Mukamal et al[5] concluderen: "Among men, consumption of alcohol at least three to four days per week was inversely associated with the risk of myocardial infarction. Neither the type of beverage nor the proportion consumed with meals substantially altered this association. Men who increased their alcohol consumption by a moderate amount during follow-up had a decreased risk of myocardial infarction."
   Rimm et al[6] concluderen in hun meta analyse: "Although most ecological studies support the hypothesis that wine consumption is most beneficial, the methodological problems of these studies limit their usefulness in drawing conclusions. Most of the differences in findings regarding specific drink types are probably due to differences in patterns of drinking specific types of alcoholic drink and to differing associations with other risk factors. Results from observational studies, where individual consumption can be assessed in detail and linked directly to coronary heart disease, provide strong evidence that a substantial proportion of the benefits of wine, beer, or spirits are attributable primarily to the alcohol content rather than to other components of each drink."
   Cleophas[7] concludeert uit zijn systematische review: "1. Small doses of alcohol (1-4 drinks a day) are associated with a slightly reduced risk of mortality and coronary heart disease (CHD). 2. Small doses (1-4 drinks a day) of wine, beer, and spirits are equally beneficial. 3. Apart from a direct beneficial effect of low doses of alcohol on mortality and CHD, some psychological factors may contribute to its beneficial effect."
   Tolstrup en Gronbaek concluderen in hun review[8]: Finally, there is some evidence that wine may have more beneficial effects than beer and distilled spirits; however, these results are still controversial and may be confounded by personal characteristics and other lifestyle factors such as diet. The inverse association between alcohol intake and CHD is influenced by age, gender, drinking pattern, and possibly by type of alcohol.

Klatsky et al[9] concluderen: We conclude that (1) drinking ethyl alcohol apparently protects against coronary disease, and (2) there may be minor additional benefits associated with drinking both beer and wine, but not especially red wine...etc.

5. Het is te verwachten dat de conclusies getrokken in de achtergronddocumenten 'alcohol' en 'alcoholhoudende dranken' met betrekking tot totale sterfte en coronaire hartziekten (paragrafen 3.2 en 3.3) overeenkomen tussen alcohol en wijn, maar niet tussen alcohol en bier en gedistilleerd; er zijn immers meer studies uitgevoerd naar de effecten van wijnconsumptie dan dat er studies zijn uitgevoerd naar de effecten van bier- en gedistilleerdconsumptie.

   De conclusies in het achtergronddocument 'alcoholhoudende dranken' in de paragrafen 3.2 en 3.3 zijn gebaseerd op een enkele meta analyse[10] die een uitgebreidere versie is van een eerdere meta analyse door grotendeels dezelfde groep epidemiologen[11]. Door de uitbreiding van de meta analyse komen de auteurs tot een herziene conclusie. Costanzo et al[10] concluderen (zie abstract van[10]): "In previous studies evaluating whether different alcoholic beverages would protect against cardiovascular disease, a J-shaped relationship for increasing wine consumption and vascular risk was found; however a similar association for beer or spirits could not be established. An updated meta-analysis on the relationship between wine, beer or spirit consumption and vascular events was performed. ..... From 16 studies, evidence confirms a J-shaped relationship between wine intake and vascular risk. ..... **Similarly, from 13 studies a J-shaped relationship was apparent for beer**.(..). From 12 studies reporting separate data on wine or beer consumption, two closely overlapping dose–response curves were obtained (maximal protection of 33% at 25 g/day of alcohol). **This meta-analysis confirms the J-shaped association between wine consumption and vascular risk and provides, for the first time, evidence for a similar relationship between beer and vascular risk.** In the meta analysis of 10 studies on spirit consumption and vascular risk, no J-shaped relationship could be found.

   De auteurs melden in de discussie bovendien dat, data voor bier- en gedistilleerdconsumptie nog steeds beperkt zijn: "Unfortunately, the very limited data available about either beer or spirit consumption in relation to cardiovascular or total mortality, did not allow us to perform a fully meta-analytic investigation on the latter two beverages."

   De conclusie geformuleerd door de auteurs is dus anders dan de conclusie weergegeven in het achtergronddocument (paragraaf 3.3.1). Deze laatste is gebaseerd op een andere analyse, een deelanalyse, uit hetzelfde artikel. Het is vooralsnog onduidelijk waarom het achtergronddocument deze analyse volgt en op basis van deze analyse de relatie tussen bierconsumptie en hart- en vaatziekten risico aanduidt als een onwaarschijnlijk verband en niet de uiteindelijke conclusie van de auteurs volgt.

   De in paragraaf 3.2 gerefereerde studie van Ferrari et al[4] betreft met name wijndrinkers; +/- 112.000 wijndrinkers tegenover +/- 31.000 bierdrinkers. Negentig procent van de vrouwen tegenover ongeveer vijftig procent van de mannen in deze studie worden gekenmerkt als wijndrinker.

6. Een derde belangrijke methodologische kanttekening wordt terecht gemaakt op pagina 7, namelijk dat er kritische opmerkingen zijn gemaakt over de controle groepen (geheelonthouder) in cohortonderzoeken (Fillmore et al[12]) naar de associatie tussen alcohol en ziekte uitkomsten. Het is echter voor de volledigheid goed te vermelden dat cohorten die wel een onderscheid hebben kunnen maken tussen niet-drinkers en ex-drinkers in hun controle groep, geen essentiële verschillen vonden in de beschreven associaties[13-16]. Het 'sick quitters' argument lijkt dus niet te gelden. Ook wanneer de controle niet uit geheelonthouders bestaat maar uit lichte drinkers zijn er verdere dalingen van het risico beschreven[17,18].

7. Met betrekking tot het interventieonderzoek, begrijpen we de keuze voor de intermediairen (bloeddruk, LDL cholesterol en BMI) zoals die wordt omschreven in het document 'werkwijze van de commissie richtlijnen goede voeding 2015'. Wij betreuren de gekozen benadering echter in het geval van dit specifieke achtergronddocument.
   HDL cholesterol verhoging, c.q. HDL gemedieerde cholesterol efflux[19] en andere HDL functies worden niet meegewogen in het hoofdstuk 2: Interventieonderzoek. Deze keuze is gemaakt omdat medicijnen en niacine die HDL cholesterol verhogen, niet aantoonbaar bijdragen aan het voorkomen van hartaanvallen. Er zijn echter een beperkt aantal geneesmiddelen getest dat HDL holesterol verhoogt, c.q. HDL functie verbetert en alcohol (net als lichamelijke activiteit) is een van de weinige nutriënten die niet alleen HDL cholesterol verhoogt maar ook zijn beschermende functies positief beïnvloedt[20-23]. HDL wordt in dezelfde mate verhoogd door bier, wijn en gedistilleerd[22,24], evenals de meeste andere intermediairen zoals gerapporteerd in de meta-analyse van Brien[24].
   Bovendien wordt door het volgen van de cases geëvalueerd door het IOM[25] een aantal andere belangrijke factoren die een causaal verband aannemelijk maken, zoals fibrinogeen en HbA1c niet geëvalueerd.
   Door deze benadering kan de commissie geen conclusie trekken over de effecten van alcoholhoudende dranken op geen enkele intermediair (zelfs niet LDL cholesterol, noch bloeddruk). Interventie onderzoek maakt echter zeer aannemelijk dat er een causaal verband is tussen consumptie van matige hoeveelheden alcoholhoudende dranken en een lagere incidentie van hart- en vaatziekten, zoals besproken in een systematisch review en meta-analyse[24] en cohort studies[26].

8. In het werkwijze document wordt gesteld dat de commissie zich in beginsel beperkt in haar literatuuronderzoek tot een kritische evaluatie van gepoolde analyses, meta-analyses en systematische reviews die gepubliceerd zijn in peer-reviewed tijdschriften. In gepoolde analyses en meta-analyses worden de bevindingen uit meerdere oorspronkelijke onderzoeken met overeenkomstige vraagstelling en aanpak gecombineerd tot een nieuwe risicoschatting.
   Echter de conclusies met betrekking tot totale sterfte zijn gebaseerd op één multicenter studie[4], die wellicht voldoet aan het criterium 'gepoolde analyse', maar niet aan het criterium 'bevindingen uit meerdere oorspronkelijke onderzoeken gecombineerd tot een nieuwe risicoschatting'. Toch wordt de bewijskracht als 'groot' omschreven.

9. Het is opvallend dat met betrekking tot Diabetes Mellitus type 2 (paragraaf 3.4), op basis van het onderzoek van Beulens et al[27] het achtergronddocument conclusies trekt over de verschillende dranktypen, terwijl de auteurs conclusies trekken over 'moderate alcohol consumption' en niet over drank specifieke effecten. De auteurs merken in hun discussie op: "The specific risk reduction associated with wine consumption, however, appears to contradict the findings of several mechanistic studies. It was previously shown that the reduced risk of diabetes with moderate alcohol consumption can be explained by increased adiponectin concentrations for 25–30%[28]. However, randomized trials in study populations consuming a variety of alcoholic beverages could not detect a difference in the effects on adiponectin concentrations[29-32]. This suggests that the underlying biological mechanism is most probably explained by alcohol itself. The specific risk reduction observed with wine could thus be attributed to other factors associated with wine consumption. Previous studies have shown that wine drinkers differ from drinkers of other beverages by consuming a healthier diet and being less likely to smoke[33]. As men and women may also differ with regard to such health-related behaviours, as is seen in the different structure of confounders amongst men and women, this could in part explain the specific association observed for wine consumption and the different effects between men and women.

10. In paragraaf 3.4 wordt herhaaldelijk gerefereerd aan 'aanvullend onderzoek' van Cullmann[34] en telkens wordt vermeld dat het onderzoek een te beperkt aantal cases betreft om daar conclusies op te baseren. Wellicht kan dit onderzoek worden verwijderd of minder worden benadrukt.

We hopen met bovenstaand commentaar een constructieve bijdrage te hebben geleverd aan het Concept Achtergronddocument richtlijnen goede voeding 2015 – Alcoholhoudende dranken.

Met vriendelijke groet,

Peter de Wolf

Directeur STIVA

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Van: Lex Lemmers
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Aan: GR_RGV2015

Onderwerp: Vijfde commentaarronde Richtlijnen goede voeding 2015 achtergronddocument Alcoholhoudende dranken

Aan de gezondheidsraad,

Dank voor het bieden van de mogelijkheid om commentaar te leveren op het achtergronddocument *Alcoholhoudende dranken* in het kader van de herziening van de *Richtlijnen Goede Voeding*. Namens het Trimbos-instituut wil ik graag onderstaande punten bij u onder de aandacht brengen.

Als eerste zijn we verbaasd dat de relatie tussen alcohol en borstkanker als niet eenduidig wordt gekenmerkt. We zijn benieuwd wat u precies bedoelt met niet eenduidig. Volgens onze lezing van de literatuur is de relatie tussen borstkanker en alcoholconsumptie wel eenduidig en dit is onder andere gebaseerd op bijgevoegde literatuur.

De vraag of gedistilleerd, bier of wijn van invloed is op de morbiditeit in het algemeen en kanker in het bijzonder lijkt ons moeilijk te beantwoorden op basis van epidemiologisch onderzoek. Een standaardglas gedistilleerd, bier of wijn bevat allemaal een zelfde hoeveelheid pure alcohol (10 gram in Nederland) en hoewel verschillend qua concentratie alcohol in de drank, leiden ze tot een zelfde BAC in het lichaam. De stof alcohol en het afbraakproduct van alcohol acetaldehyde worden beiden als carcinogeen aangemerkt. Hoewel consumenten voorkeur kunnen hebben voor een specifieke alcoholhoudende drank (wijn, bier of gedistilleerd), worden in de praktijk diverse alcoholhoudende dranken door elkaar heen gedronken (bijvoorbeeld wijn in combinatie met een aperitief en cognac).

Met vriendelijke groet,

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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

Collaborative Group on Hormonal Factors in Breast Cancer*[1]

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Epidemiology

Alcohol and tobacco consumption are closely correlated and published results on their association with breast cancer have not always allowed adequately for confounding between these exposures. Over 80% of the relevant information worldwide on alcohol and tobacco consumption and breast cancer were collated, checked and analysed centrally. Analyses included 58 515 women with invasive breast cancer and 95 067 controls from 53 studies. Relative risks of breast cancer were estimated, after stratifying by study, age, parity and, where appropriate, women's age when their first child was born and consumption of alcohol and tobacco. The average consumption of alcohol reported by controls from developed countries was 6.0 g per day, i.e. about half a unit/drink of alcohol per day, and was greater in ever-smokers than never-smokers, (8.4 g per day and 5.0 g per day, respectively). Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 (1.19–1.45, $P<0.00001$) for an intake of 35–44 g per day alcohol, and 1.46 (1.33–1.61, $P<0.00001$) for $\geqslant$45 g per day alcohol. The relative risk of breast cancer increased by 7.1% (95% CI 5.5–8.7%; $P<0.00001$) for each additional 10 g per day intake of alcohol, i.e. for each extra unit or drink of alcohol consumed on a daily basis. This increase was the same in ever-smokers and never-smokers (7.1% per 10 g per day, $P<0.00001$, in each group). By contrast, the relationship between smoking and breast cancer was substantially confounded by the effect of alcohol. When analyses were restricted to 22 255 women with breast cancer and 40 832 controls who reported drinking no alcohol, smoking was not associated with breast cancer (compared to never-smokers, relative risk for ever-smokers=1.03, 95% CI 0.98–1.07, and for current smokers=0.99, 0.92–1.05). The results for alcohol and for tobacco did not vary substantially across studies, study designs, or according to 15 personal characteristics of the women; nor were the findings materially confounded by any of these factors. If the observed relationship for alcohol is causal, these results suggest that about 4% of the breast cancers in developed countries are attributable to alcohol. In developing countries, where alcohol consumption among controls averaged only 0.4 g per day, alcohol would have a negligible effect on the incidence of breast cancer. In conclusion, smoking has little or no independent effect on the risk of developing breast cancer; the effect of alcohol on breast cancer needs to be interpreted in the context of its beneficial effects, in moderation, on cardiovascular disease and its harmful effects on cirrhosis and cancers of the mouth, larynx, oesophagus and liver.
British Journal of Cancer (2002) **87,** 1234–1245. doi:10.1038/sj.bjc.6600596 www.bjcancer.com

Keywords: breast cancer; alcohol; tobacco; smoking; collaborative reanalysis

Many epidemiological studies have investigated the relationship between breast cancer and the consumption of alcohol and/or tobacco. References to over 80 studies that have collected relevant data, as well as to reviews of the subject, are given in Appendix II (www.bjcancer.com). The published results from these studies have generally suggested that women who regularly consume alcohol may be at a slightly increased risk of the disease, but the findings reported for tobacco are inconsistent. Alcohol and tobacco consumption are known to be associated one with another, and published results have not always allowed adequately for possible confounding between these exposures. Individual data from 65 epidemiological studies of breast cancer 63 published[1–63] and two unpublished in which information on alcohol and/or tobacco consumption had been collected contributed to this collaboration. These studies, some of which have not published results for alcohol or tobacco, include over 80% of the worldwide information on the topic (see Appendix II (www.bjcancer.com)). The data from these studies were analysed, taking careful account of the possible confounding between alcohol and tobacco consumption, as well as confounding by other factors.

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METHODS

Eligibility of studies and collection of data

Data from epidemiological studies of women with breast cancer have been brought together by the Collaborative Group on

Hormonal Factors in Breast Cancer to describe the relationship between breast cancer and various reproductive, hormonal and other factors.[64,65] Case–control and cohort studies were eligible for the collaboration if they included at least 100 women with incident invasive breast cancer and recorded information on reproductive factors and on use of hormonal therapies. Cohort studies were included using a nested case–control design, in which four controls were selected at random, matched on follow-up to the age of the case at diagnosis and, where appropriate, broad geographical region. Data for individual women were collated and analysed centrally so that analyses could be carried out using as similar definitions across studies as was possible. Details sought from principal investigators of each participating study included data that had been collected on each woman's reproductive history and various other factors that may be relevant to the aetiology of breast cancer, including the women's consumption of alcohol and tobacco.

Some investigators provided estimates of alcohol intake reported by each woman expressed as gram (g) of alcohol consumed per day or per week. Others provided information on the reported number of alcoholic drinks consumed daily or weekly. In such instances, the number of grams of alcohol consumed per day, was estimated assuming that one alcoholic drink contains 12 g alcohol in the USA and Italy,[11] 8 g in the UK and 10 g elsewhere (Brewers' Society, personal communication). No information was sought about alcohol consumption at various ages or about the particular type of alcohol consumed. Information was also sought on whether or not each woman had ever smoked, and whether she was a current or past smoker. Active smoking only was considered and no attention given to the reported associations with environmental tobacco smoke,[35,49] nor was information sought on the age women were when smoking started or stopped, or on the amount smoked. The methods of identifying studies and of data checking, and correction, have been described elsewhere.[64,65]

Statistical analysis and presentation of results

Statistical methods were similar to those used in previous reports by this group.[64–67] Data from different studies were combined by means of the Mantel–Haenszel stratification technique, the stratum-specific quantities calculated being the standard 'observed minus expected' (O–E) numbers of women with breast cancer, together with their variances and covariances. These values yield both statistical descriptions (odds ratios, subsequently referred to as relative risks) and statistical tests (*P* values). When only two groups are being compared, relative risk estimates are obtained from O–E values by the one-step method,[66] as are their standard errors (SE) and confidence intervals (CI). When more than two groups are compared, variances are estimated by treating the relative risks as floating absolute risks (FARs).[67] This approach yields floated standard errors (FSE) and floated confidence intervals (FCI). Presentation of the results in this way enables valid comparisons between any two exposure groups, even if neither is the baseline group. Any comparison between groups must take the variation in each estimate into account by summing the variances of the logarithms of the two FARs.

To obtain comparability between the women with breast cancer and similar women without breast cancer, all analyses were routinely stratified by study, and centre within study; by age (in single years from 16 to 64, 65 to 69, 70 to 74, etc., up to 85 to 89); by parity and, where appropriate, age when the first child was born (nulliparous women were assigned to a separate stratum and parous women were cross-classified according to parity (1–2, 3–4, 5–6, 7+) and age at first birth (<20, 20–24, 25–29, 30+)). Where appropriate analyses relating to alcohol consumption were stratified by smoking history (ever/never) and analyses relating to tobacco consumption were stratified by alcohol consumption (0, <5, 5–14, 15–24, 25–34, 35–44, ⩾45 g per day). In order to summarise the relationship between alcohol consumption and breast cancer risk, a linear trend in the log relative risk of breast cancer was fitted across increasing categories of consumption. In estimating such trends, the median consumption within a given category was taken to be the level of alcohol consumption for that category.

In general, results in the text are presented as relative risks and their appropriate SE or FSEs. Where results are presented in the form of plots, relative risks and their corresponding CIs/FCIs are represented by squares and lines, respectively. The position of the square indicates the value of the relative risk and its area is inversely proportional to the variance of the logarithm of the relative risk, thereby providing an indication of the amount of statistical information available for that particular estimate. Owing to the large number of relative risk estimates calculated, results are given with their appropriate 99% CIs/FCIs; and 95% CIs/FCIs are used only to summarise the main findings.

The absolute risk of breast cancer associated with various levels of alcohol consumption was estimated for women in developed countries, by applying the dose-response estimates obtained here to age-specific incidence rates for breast cancer in developed countries around 1990[64,65] assuming that an intake of 10 g per day is roughly equivalent to one unit or drink of alcohol per day. The cumulative incidence of breast cancer up to age 80 years was calculated from the age-specific findings.

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RESULTS

The 65 studies that contributed individual data on alcohol and/or tobacco consumption and other factors relevant to breast cancer included a total of 66 426 women with invasive breast cancer (cases) and 126 953 women without breast cancer controls from 63 published[1–63] and two unpublished studies. Information on both alcohol and tobacco had been collected in 53 of these studies, that included a total of 58 515 cases and 95 067 controls from 51 published[1–51] and two unpublished studies. Unless otherwise specified, analyses presented here are restricted to data from these 53 studies. This enables women to be cross-classified by both their alcohol and tobacco consumption, thus permitting adequate examination of possible confounding between the two exposures.

Among women with breast cancer in the 53 studies included in the main analyses, the median year of diagnosis was 1988 and the average age at diagnosis was 52.1 years. All but five of the 53 studies[5,9,21,41,48] were conducted in developed countries. Among controls, alcohol consumption was substantially greater in women from developed than developing countries (average alcohol intakes of 6.0 g per day and 0.4 g per day, respectively). The proportion of controls from developed countries who reported drinking no alcohol was 40%, and a further 28% reported consuming <5 g per day, i.e. less than half a unit/drink of alcohol per day (Table 1). Only about 1% of the controls from developed countries reported drinking 35–44 g per day alcohol, i.e. about four units or drinks daily, and a similar proportion reported drinking ⩾45 g per day.

Overall about half the women in developed countries reported that they had ever smoked, but smoking habits varied considerably according to alcohol intake, both for cases and controls (Table 1). Among controls from developed countries who reported drinking no alcohol, 37% had ever smoked, and the proportion of ever-smokers increased with increasing intake of alcohol, rising to 73% for controls who reported drinking ⩾45 g per day alcohol (Table 1). The average alcohol consumption reported by ever-smokers from developed countries was greater than that reported by never-smokers (8.4 g per day *vs* 5.0 g per day).

Table 1 Reported alcohol and tobacco consumption among cases and controls in developed countries for whom information on both factors was available

	Alcohol consumption (g per day)							
	0	1–4	5–14	15–24	25–34	35–44	45+	Total
CASES								
Number (%)	18331 (36)	13785 (27)	10238 (20)	3444 (6.8)	2522 (5.0)	954 (1.9)	1192 (2.4)	50466 (100)
Per cent that ever-smoked	39%	48%	58%	60%	56%	64%	70%	49%
CONTROLS								
Number (%)	31872 (40)	22654 (28)	15484 (19)	5082 (6.3)	2727 (3.4)	1119 (1.4)	1067 (1.3)	80005 (100)
Per cent that ever-smoked	37%	46%	55%	62%	60%	66%	73%	46%

Table 2 Relative risk[a] of breast cancer in relation to reported intake of alcohol, according to smoking history

g per day alcohol consumption (median)	Never-smoker relative risk[a] (FSE)	Ever-smoker relative risk[a] (FSE)	All women relative risk[a] (FSE)
0 (0)	1.00 (0.015)	1.00 (0.018)	1.00 (0.012)
<5 (2)	1.01 (0.020)	1.01 (0.020)	1.01 (0.014)
5–14 (8)	1.01 (0.023)	1.05 (0.021)	1.03 (0.015)
15–24 (18)	1.19 (0.048)	1.09 (0.035)	1.13 (0.028)
25–34 (29)	1.22 (0.056)	1.19 (0.047)	1.21 (0.036)
35–44 (39)	1.18 (0.093)	1.40 (0.077)	1.32 (0.059)
⩾45 (58)	1.49 (0.110)	1.46 (0.072)	1.46 (0.060)
Increase in the relative risk of breast cancer per 10 g per day (SE)	7.1% (1.3%)	7.1% (0.9%)	7.1% (0.8%)

[a]Calculated as floating absolute risk (FAR), with corresponding floated standard error (FSE), and stratified by study, age, parity, age at first birth and, for 'all women', by smoking history (see Methods).

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Because alcohol and tobacco consumption are so closely associated, analyses of their effects were initially carried out separately for never-smokers and ever-smokers (in the case of alcohol) and for drinkers and non-drinkers (in the case of tobacco).

Breast cancer in relation to alcohol consumption

Table 2 shows the relative risks and corresponding standard errors for breast cancer according to women's reported daily intake of alcohol for never-smokers and ever-smokers. In each group the relative risk of breast cancer increased significantly with increasing intake of alcohol, increasing by the same amount, 7.1%, for each additional 10 g per day intake of alcohol ($P<0.00001$ in each group). The trends associated with increasing levels of alcohol intake in never-smokers and ever-smokers did not differ significantly from each other (χ^2_1 for heterogeneity=0.002; $P=1.0$). Therefore subsequent analyses concerning alcohol consumption include both never-smokers and ever-smokers, and the data are stratified by smoking history as well as by study, age, parity and age at first birth.

When the data in smokers and non-smokers were combined the relative risk of breast cancer increased with alcohol intake, increasing by 7.1% (SE 0.8%; $P<0.00001$) for each additional 10 g per day intake of alcohol, i.e. for each extra unit/drink of alcohol consumed on a daily basis (Figure 1). Compared to women who drank no alcohol the relative risk was 1.32 (0.059, $P<0.00001$) for women whose reported alcohol consumption was 35–44 g per day and 1.46 (0.060, $P<0.00001$) for a consumption of ⩾45 g per day, where the average consumption was 57 g per day.

The study-specific results are summarised in Figure 2, grouped according to study design. Studies which contributed the smallest amounts of statistical information, were grouped together as 'other' in each of these categories. There was no strong evidence to suggest that the results varied substantially across studies ($\chi^2_{52}=60.7$; $P=0.3$) or according to study design (χ^2_2 for heterogeneity=1.5; $P=0.5$). In the one study[52] which contributed data on alcohol, but not smoking, the estimated increase in the relative risk of breast cancer per additional 10 g per day intake was 13.8% (SE 10.5%). Because of the large standard error, the estimated increase in relative risk in this study does not differ significantly from results for all other studies combined ($\chi^2_1=0.4$, $P=0.5$).

The effect of adjusting for 11 other potential confounding factors (race, education, family history of breast cancer, age at menarche, height, weight, body mass index, breastfeeding, use of hormonal preparations, and age at and type of menopause) on the relationship in Figure 1 is shown in Table 3. Additional adjustment for each of these factors in turn did not materially alter the magnitude of the increase in the relative risk of breast cancer associated with increasing levels of alcohol intake, suggesting that the associations in Figure 1 are not much confounded by any of them.

Breast cancer in relation to tobacco consumption

Among the 22 255 cases and 40 832 controls who reported drinking no alcohol, the risk of breast cancer in ever-smokers did not differ significantly from that in never-smokers (relative risk for ever *vs* never-smokers=1.03, SE 0.023; NS). However, among women who reported drinking alcohol, the findings for smoking were difficult to disentangle from the effects of the alcohol itself. When ever-smokers were compared to never-smokers the relative risk for breast cancer was 1.09 (0.018) before stratification by the amount of alcohol consumed, and declined to 1.05 (0.020) after stratification. The corresponding χ^2_1 value declined by three-quarters from 23.4 to 6.4. Since alcohol consumption is known to be unreliably measured,[68] and stratification for such a poorly measured variable reduced the χ^2 value by three-quarters, stratification by true alcohol intake would be expected to reduce the χ^2 value by even more.[69] Since it is not possible to eliminate residual confounding among drinkers, results concerning tobacco consumption are restricted to women who reported drinking no alcohol at all, where such confounding should be minimised.

The study-specific relative risks for breast cancer in ever-smokers compared to never-smokers are shown in Figure 3, for women who reported drinking no alcohol. There was no marked variation in the relative risk of breast cancer across studies ($\chi^2_{52}=58.0$, $P=0.3$) or study design ($\chi^2_2=6.1$, $P=0.05$). Information on current and past smoking was available for all but five studies.[2,23,28] (and two unpublished). Among ever-smokers in the remaining 48 studies 54% were current smokers and 46% were past smokers. Compared to never-smokers the relative risk of breast cancer was 0.99 (SE 0.03) for current smokers (Appendix III (www.bjcancer.com)), and 1.07 (SE 0.03) for past smokers (Appendix IV (www.bjcancer.com)).

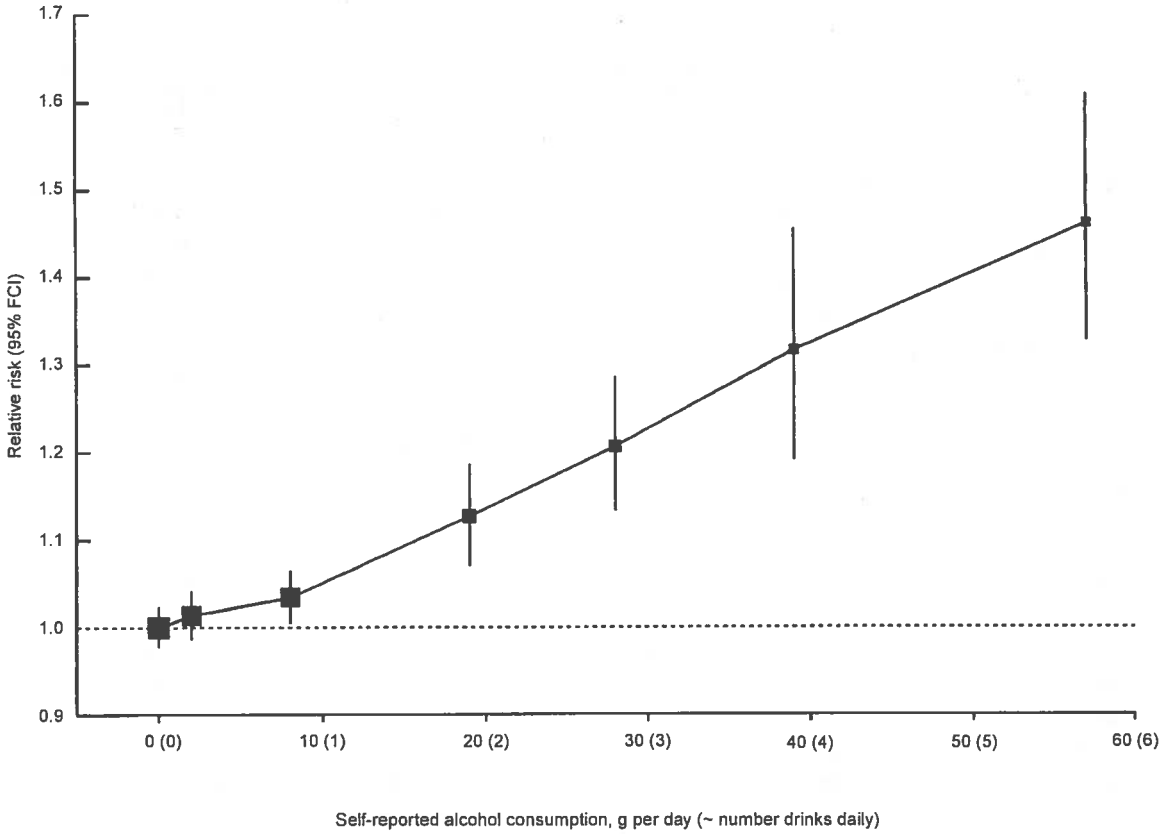

Figure 1 Relative risk of breast cancer in relation to reported intake of alcohol. Relative risks are calculated as floating absolute risk (FAR) and stratified by study, age, parity, age at first birth and smoking.

Among controls from developed countries a greater proportion of ever-smokers than never-smokers had had a bilateral oophorectomy (8.7% *vs* 7.6%) or a hysterectomy without bilateral oophorectomy (13.3% *vs* 12.5%). The average age at bilateral oophorectomy was 41.6 (SD 7.5) and 44.2 (SD 6.6), respectively and the average age at hysterectomy was 38.6 (SD 9.3) and 40.0 (SD 9.9), respectively. Average age at natural menopause was also slightly earlier in ever-smokers than in never smokers, at 48.3 (SD 4.8) and 49.3 (SD 4.7) years, respectively. The relative risk of breast cancer in ever *vs* never-smokers was similar for women who had had an oophorectomy, hysterectomy or natural menopause (Table 4) and additional stratification by age at and type of menopause did not materially alter the overall magnitude of the relative risk (Table 3). Nor did additional stratification by 10 other potential confounding factors much alter the relative risk.

Eleven studies[53–63] that together included a total of 4781 cases and 12713 controls, contributed data to this collaboration on tobacco consumption for each woman, but not on alcohol consumption. The combined relative risk of breast cancer in ever-smokers compared to never-smokers in these 11 studies was 1.05 (SE 0.05), but because of the potential for confounding by alcohol the results from these studies have not been included in the main analyses.

Consistency of the findings

The increase in the relative risk of breast cancer for each additional 10 g per day intake of alcohol consumption was calculated separately for various subgroups of women, subdivided according to 15 personal characteristics including their age, childbearing pattern, race and familial patterns of breast cancer. Overall there was no significant variation in the trend associated with increasing intake of alcohol between categories defined by any of the 15 factors examined (Figure 4: global test for heterogeneity $\chi^2_{15}=18.0$; $P=0.3$). Nor was there significant variation in the relative risk of breast cancer associated with having ever smoked across categories of the 15 characteristics examined (Figure 4: global test for heterogeneity $\chi^2_{15}=17.9$; $P=0.3$).

Information on the extent of spread of the breast cancer was available for about 60% of the study population. Both for tumours localised to the breast and for tumours that had spread beyond the breast, the risk of breast cancer increased with increasing alcohol consumption (increase in relative risk of breast cancer of 6.9% (1.3%) and 9.4% (1.5%), respectively, per 10 g per day alcohol consumption: $\chi^2_1=3.3$; $P=0.07$). There was no significant difference in the extent of tumour spread among the cases according to tobacco consumption ($\chi^2_1=3.0$, $P=0.08$).

Cumulative incidence of breast cancer

Around 1990 the cumulative incidence of breast cancer up to age 80 years was between about eight and 10 per 100 women in developed countries.[64,65,70] The average consumption of alcohol by controls studied here from developed countries was 6.0 g per day. If the dose-response relationship described here is valid, it is

Study(Country)[ref.]	Number Cases/Controls	Mean intake of alcohol (g/day) Cases/Controls	% increase in relative risk per 10g/day intake of alcohol (SE)
COHORT STUDIES:			
Nurses Health Study(USA)[6]	2870/11480	6.3/5.2	4.4 (2.5)
Canadian NBSS(Canada)[24]	753/2857	9.2/8.9	1.2 (4.1)
American Cancer Society(USA)[51]	1196/4829	9.5/9.0	7.0 (5.3)
Netherlands Cohort(Netherlands)[33]	470/1686	6.3/5.8	2.8 (6.9)
Iowa Womens Health(USA)[19]	1188/4752	4.1/3.5	8.1 (4.8)
Million Women Study(UK)[47]	1436/5744	5.6/5.2	9.8 (6.3)
Other[1,13,26,41]	1780/7083	0.8/0.4	34.7 (41.5)
All cohort studies	**9693/38431**	**5.0/ 4.4**	**5.0 (1.7)**
CASE-CONTROL, POPULATION CONTROLS:			
Brinton(USA)[3]	1726/2179	8.7/7.2	3.7 (4.0)
CASH(USA)[10]	4455/4672	8.2/7.4	3.5 (2.8)
Bernstein(USA)[44]	676/676	6.9/5.6	10.0 (7.4)
Bain/Siskind(Australia)[15]	487/981	6.7/5.6	-1.2 (9.7)
Rohan(Australia)[8]	451/451	7.0/4.5	4.9 (10.6)
Ewertz(Denmark)[17]	1525/1398	7.4/7.2	4.3 (5.0)
Long Island(USA)[38]	1183/1184	5.9/4.6	15.8 (7.7)
Clarke(Canada)[16]	607/1214	8.5/7.6	3.6 (6.8)
Paul/Skegg(New Zealand)[18]	888/1857	3.8/3.4	7.3 (11.4)
Daling(USA)[29]	747/961	7.4/6.8	-0.6 (5.2)
Ross/Paganini-Hill(USA)[31]	1055/1092	7.7/6.5	8.6 (5.3)
UK studies(UK)[28+2 unpublished]	1871/1871	5.6/5.8	1.2 (5.1)
4 State Study(USA)[30]	6880/9525	6.6/5.3	13.4 (2.2)
Rookus/van Leeuwen(Netherlands)[27]	918/918	10.6/9.6	5.6 (4.8)
Yang/Gallagher(Canada)[22]	1019/1025	4.9/5.2	1.1 (9.0)
Primic/Zakelj(Slovenia)[32]	619/619	3.7/2.0	14.5 (13.8)
Stanford/Habel(USA)[36]	450/492	6.4/5.4	-1.0 (9.8)
WISH(USA)[40]	1866/2007	6.0/6.6	-1.8 (5.4)
Magnusson(Sweden)[46]	3168/3285	2.7/2.2	19.7 (8.4)
McCredie/Hopper(Australia)[42,45]	1581/1021	6.9/6.0	8.3 (6.4)
Chang-Claude(Germany)[40]	656/1283	10.8/8.5	14.8 (5.0)
Johnson(Canada)[49]	2338/2427	5.2/6.2	6.6 (4.5)
Other[5,7,9,20,21,35,37,48]	3509/4656	2.1/2.4	9.4 (7.0)
All case-control, pop controls	**38675/45794**	**6.0/ 5.3**	**7.4 (1.1)**
CASE-CONTROL, HOSPITAL CONTROLS:			
Vessey(UK)[12]	1125/1125	3.1/3.5	-7.4 (7.6)
Franceschi(Italy)[4,43]	2929/2963	14.2/12.2	3.2 (2.6)
Lê/Gerber/Clavel(France)[2,14,39]	1204/1724	8.9/6.4	20.6 (6.3)
La Vecchia(Italy)[11]	3623/2729	17.3/14.1	9.5 (2.5)
Katsouyanni(Greece)[25]	795/1548	4.4/4.1	20.0 (13.7)
Other[23,34]	471/753	14.5/8.5	9.7 (8.4)
All case-control, hospital controls	**10147/10842**	**12.5/ 9.4**	**7.3 (1.7)**
ALL STUDIES	**58515/95067**	**7.0/ 5.4**	**7.1 (0.8)**

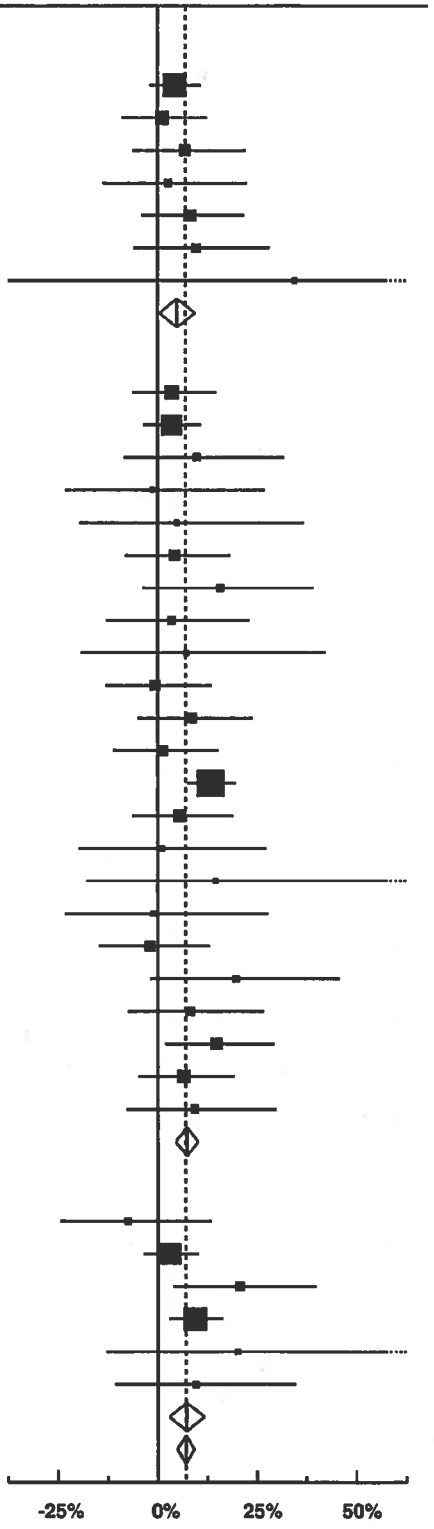

Figure 2 Details of and results from studies on the relation between alcohol consumption and breast cancer. Relative risks are stratified by age, parity, age at first birth and smoking history.

Study(Country)[ref.]	Number Cases/Controls	% ever smoked Cases/Controls	Relative risk of breast cancer in ever- versus never-smokers (SE)
COHORT STUDIES:			
Nurses Health Study(USA)[6]	1224/5599	49/49	1.01 (0.07)
Canadian NBSS(Canada)[24]	181/662	35/35	1.25 (0.23)
American Cancer Society(USA)[51]	213/922	34/33	1.07 (0.19)
Netherlands Cohort(Netherlands)[33]	119/504	27/30	0.89 (0.23)
Iowa Womens Health(USA)[19]	679/2765	25/26	0.93 (0.10)
Million Women Study(UK)[47]	324/1291	50/44	1.24 (0.15)
Other[1,13,26,41]	1923/7655	4/5	0.78 (0.12)
All cohort studies	**4663/19398**	**25/26**	**1.00 (0.04)**
CASE-CONTROL, POPULATION CONTROLS:			
Brinton(USA)[9]	649/872	29/26	1.12 (0.14)
CASH(USA)[10]	1817/1821	49/43	1.28 (0.08)
Bernstein(USA)[44]	336/317	50/48	1.18 (0.20)
Bain/Siskind(Australia)[15]	248/514	32/29	1.31 (0.26)
Rohan(Australia)[8]	188/213	35/32	1.06 (0.31)
Ewertz(Denmark)[17]	227/198	59/57	0.88 (0.27)
Long Island(USA)[38]	153/208	37/34	0.99 (0.32)
Clarke(Canada)[16]	114/211	40/42	0.88 (0.31)
Paul/Skegg(New Zealand)[18]	538/1058	43/41	1.09 (0.13)
Daling(USA)[29]	211/286	42/42	0.87 (0.21)
Ross/Paganini-Hill(USA)[31]	578/590	53/52	1.02 (0.13)
UK studies(UK)[28+2 unpublished]	655/662	47/45	1.08 (0.13)
4 State Study(USA)[30]	1507/2247	39/39	1.07 (0.09)
Rookus/van Leeuwen(Netherlands)[27]	247/247	52/51	0.90 (0.21)
Yang/Gallagher(Canada)[22]	505/517	48/44	1.15 (0.17)
Primic/Zakelj(Slovenia)[32]	115/128	29/30	0.67 (0.38)
Stanford/Habel(USA)[36]	152/181	52/49	0.79 (0.26)
WISH(USA)[40]	353/241	59/68	0.63 (0.21)
Magnusson(Sweden)[46]	1311/1312	32/33	0.91 (0.08)
McCredie/Hopper(Australia)[42,45]	774/518	38/36	1.03 (0.15)
Chang-Claude(Germany)[40]	168/251	46/52	0.94 (0.25)
Johnson(Canada)[49]	974/1110	42/40	1.14 (0.11)
Other[5,7,9,20,21,35,37,48]	2851/3567	11/13	0.99 (0.12)
All case-control, pop controls	**14671/17269**	**36/35**	**1.07 (0.03)**
CASE-CONTROL, HOSPITAL CONTROLS:			
Vessey(UK)[12]	154/171	44/53	0.71 (0.30)
Franceschi(Italy)[4,43]	831/1025	31/31	1.01 (0.12)
Lê/Gerber/Clavel(France)[2,14,39]	492/923	18/24	0.82 (0.16)
La Vecchia(Italy)[11]	980/1034	28/30	0.82 (0.10)
Katsouyanni(Greece)[25]	219/462	21/24	1.28 (0.29)
Other[23,34]	245/550	20/26	0.72 (0.25)
All case-control, hospital controls	**2921/4165**	**27/29**	**0.89 (0.06)**
ALL STUDIES	**22255/40832**	**33/30**	**1.03 (0.02)**

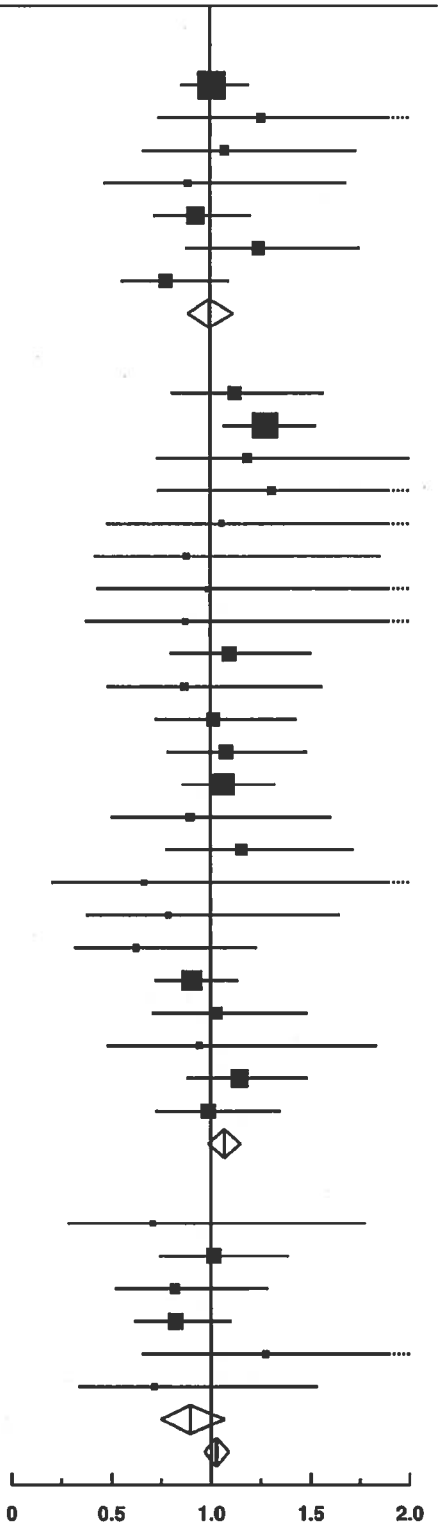

Figure 3 Details of and results on the relation between tobacco consumption and breast cancer in women who reported drinking no alcohol. Relative risks are stratified by age, parity and age at first birth.

Table 3 Effect of additional adjustment for various factors on the relative risk of breast cancer associated with alcohol and tobacco consumption

	Per cent increase (SE) in the relative risk of breast cancer per 10 g per day alcohol intake	Relative risk (SE) of breast cancer in ever-smokers, compared to never-smokers for women who reported drinking no alcohol
After stratification for study, age, parity, age at first birth and, for analyses concerning alcohol, tobacco consumption	7.1% (0.8%)	1.03 (0.02)
After additional stratification for:		
race	7.2% (0.8%)	1.03 (0.02)
education	7.3% (0.8%)	1.04 (0.03)
mother or sister with breast cancer	7.2% (0.8%)	1.02 (0.03)
age at menarche	7.4% (0.8%)	1.04 (0.03)
height	7.5% (0.8%)	1.02 (0.03)
weight	7.2% (0.8%)	1.04 (0.03)
body mass index	6.9% (0.8%)	1.04 (0.03)
breastfeeding	6.9% (0.8%)	1.02 (0.02)
ever use of hormonal contraceptives	6.6% (0.8%)	1.02 (0.03)
ever use of hormone replacement therapy	7.3% (0.8%)	1.02 (0.03)
type of and age at menopause	7.2% (0.8%)	1.06 (0.03)

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estimated that about 4% of breast cancers in developed countries are attributable to alcohol. The cumulative incidence of breast cancer by age 80 years is estimated to increase from 8.8 per 100 women in non-drinkers to 9.4, 10.1, 10.8, 11.6, 12.4 and 13.3, respectively, per 100 women consuming an average of 1, 2, 3, 4, 5 and 6 alcoholic drinks each day (see Figure 5). In developing countries, where alcohol consumption is very low, averaging only about 0.4 g per day, alcohol would make a negligible contribution to the total number of cases of breast cancer.

DISCUSSION

There is potential for confounding between the possible effects of alcohol and of tobacco on breast cancer, as drinking and smoking are closely associated, one with another. Among controls from developed countries, the proportion of ever-smokers rose from 37% in women who reported drinking no alcohol at all, to 73% in women drinking $\geqslant$45 g per day alcohol, and alcohol consumption was greater in ever-smokers than in never-smokers, averaging 8.4 and 5.0 g per day, respectively.

The relative risk of breast cancer was found to increase with increasing intake of alcohol, both in never-smokers and in ever-smokers, and the magnitude of the increase was the same in each group (an increase of 7.1% in the relative risk of breast cancer for each additional 10 g per day alcohol; 95% CI 5.5–8.7% $P<0.00001$ overall). The observed association between breast cancer and alcohol consumption is therefore unlikely to be an indirect effect of tobacco.

Conversely, the relationship between smoking and breast cancer was found to be confounded by alcohol. Among women who drank no alcohol, ever-smokers and current smokers were not at an increased risk of breast cancer compared to never-smokers. Among women who drank alcohol, however, adjustment of the relative risk of breast cancer by the amount of alcohol consumed had a substantial effect on the results and, since it is not possible to measure alcohol intake reliably and thus eliminate residual confounding due to alcohol, we chose to base our assessment of the effect of tobacco on breast cancer on the 22 255 cases and 40 832 controls recorded as drinking no alcohol at all. In this large group of women the results suggest that smoking has little or no independent effect on the risk of developing breast cancer.

The association between breast cancer and alcohol or tobacco consumption does not appear to be materially confounded by the effects of other factors. Potential confounding by age, study, parity, age at first birth and tobacco consumption were minimised by stratification. Ever-smokers had their natural menopause about 1 year earlier, on average than never-smokers and were also more likely to have had a bilateral oophorectomy or hysterectomy, but adjustment for type of and age at menopause had little effect on the relative risk of breast cancer in ever- *vs* never-smokers (Tables 3 and 4). In addition, possible confounding by race, education, family history of breast cancer, age at menarche, height, weight, body mass index, breastfeeding and use of hormonal preparations was examined by adjustment for each factor in turn, but none materially altered the estimates of relative risk (Table 3). Since the relative risk estimates for breast cancer in relation to both alcohol and tobacco consumption did not appear to differ substantially according to any of these factors, there is no strong evidence for interaction between either of these exposures and the 15 factors examined (Figure 4).

There was no significant difference in the extent of tumour spread according to either alcohol or tobacco consumption, suggesting that there is little differential detection of breast cancer or effect on tumour growth by these exposures.

Combining results from different studies

Combining results across many studies has the advantage of yielding estimates of the relative risk that are not subject to as much

Table 4 Relative risk of breast cancer in ever *vs* never smokers, according to menopausal status, in women who reported drinking no alcohol. Relative risks are stratified by study, age, panty and age at first birth

Menopausal status	Relative risk (SE)
Premenopausal	1.07 (0.05)
Natural menopause	
before age 45 years	1.11 (0.15)
at age 45–49 years	0.98 (0.08)
at age $\geqslant$50 years	1.12 (0.06)
Bilateral oophorectomy	
before age 45 years	0.78 (0.16)
at age $\geqslant$45 years	0.82 (0.15)
Hysterectomy before menopause	1.08 (0.09)

χ^2_6 for heterogeneity=7.5; P=0.9

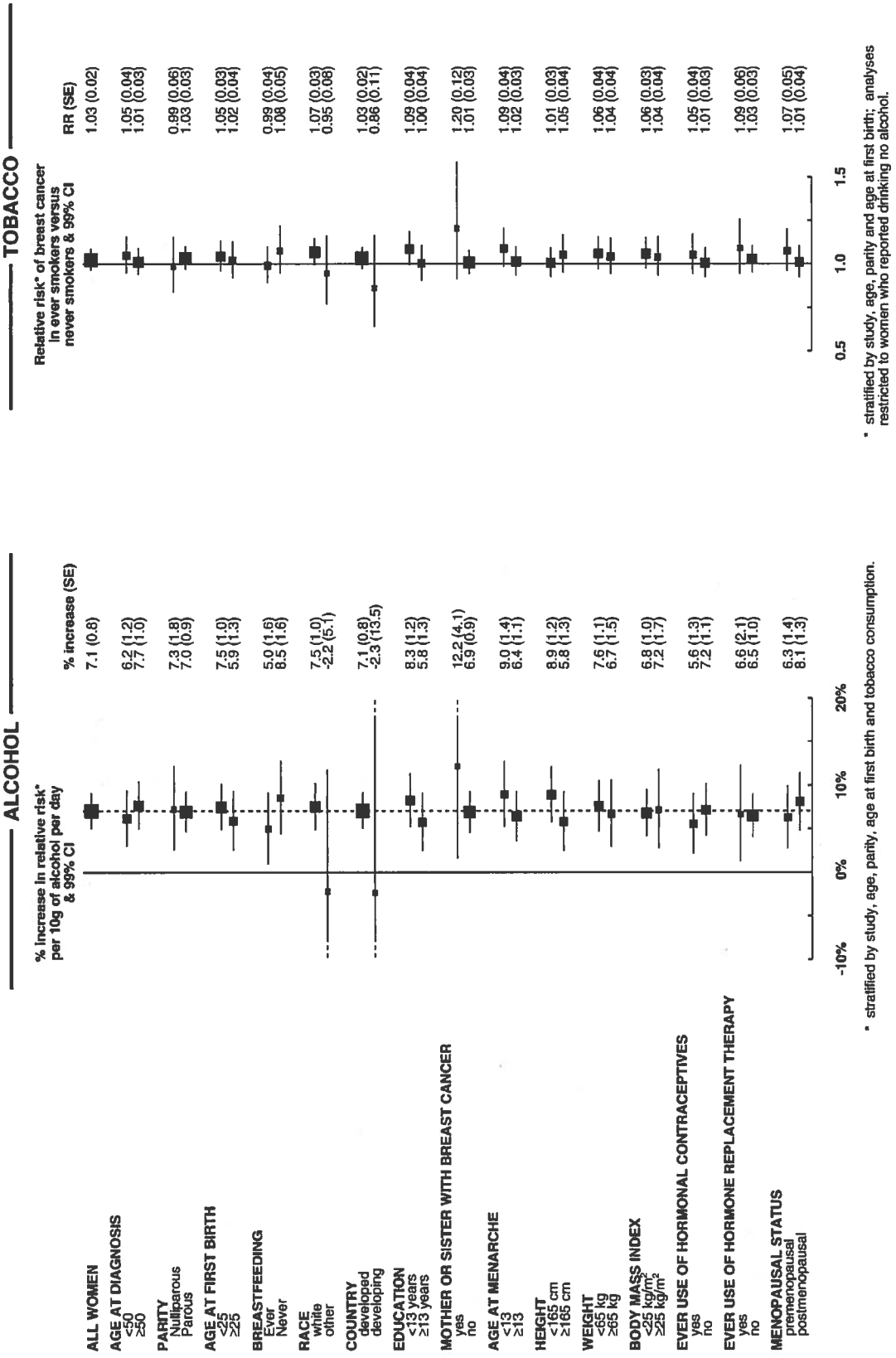

Figure 4 Relative risk of breast cancer in relation to alcohol and tobacco consumption in various subgroups of women.

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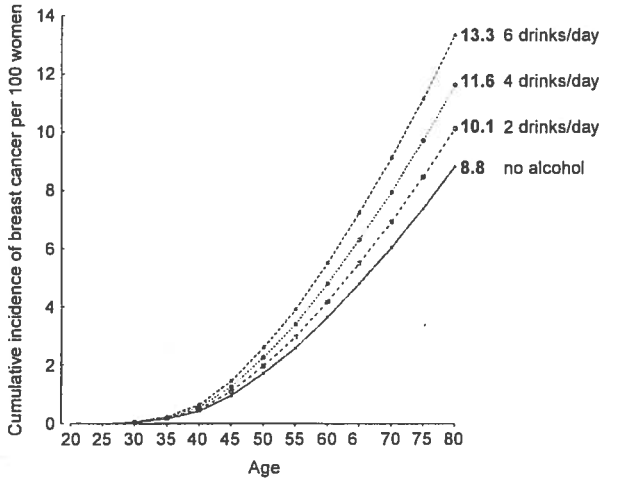

Figure 5 Estimated cumulative incidence of breast cancer per 100 women in developed countries, according to the number of alcoholic drinks consumed each day (see Methods).

random fluctuation as that found in any individual study. The studies that contributed to these findings were of different designs and included women with a wide range of alcohol and tobacco consumption and of other personal characteristics. Nevertheless, the relationships between breast cancer and alcohol and tobacco were seen consistently across studies and study designs, and for women of different ages, different childbearing histories, and for women who differed according to various other personal characteristics. The results were not unduly influenced by any particular study or groups of studies.

Because of the strong association between alcohol and tobacco consumption, the main analyses were restricted to data from the 53 studies in which information on both exposures had been collected in the same women. Results from the only study[52] that had provided individual data on alcohol, but not tobacco, did not differ significantly from the overall findings for breast cancer and alcohol. The remaining 11 studies[53–63] that provided individual data on tobacco, but not on alcohol, could not contribute directly to this review, since it was not possible to take into account for the important confounding effect of alcohol. None of the publications from these 11 studies has, however, claimed that smoking affected the risk of breast cancer.

As far as can be ascertained, over 80% of the worldwide epidemiological data that have been assembled on the relationship between breast cancer and alcohol and tobacco consumption were contributed to this collaboration. Another 20 studies were identified with relevant data that together included about 12 000 women with breast cancer (see Appendix II (www.bjcancer.com)), but because results were presented in a different way in each study, it is difficult to combine the published data directly. Nevertheless, out of the six largest studies all but one (reference number 66, in Appendix II (www.bjcancer.com)) reported a statistically significant increased risk of breast cancer with increasing intake of alcohol. Each of these six studies included at least 500 women with breast cancer and altogether they comprised most of the information that had not been contributed in this collaboration. The remaining 14 studies were comparatively small and none of their published results on alcohol differed substantially from those reported here. Therefore the findings on alcohol and breast cancer from studies not included here do not appear to differ materially from these results.

Only one of the 20 studies that had not contributed to this collaboration claimed that smoking is associated with an increased risk breast cancer (reference number 81, in Appendix II (www.bjcancer.com)). None of these studies has, however, published results on the risk of breast cancer in relation to smoking, restricted to women who never drank alcohol.

Limitations of these findings

Overall, the relative risk of breast cancer appeared to increase by 7.1% (95% CI 5.5–8.7%) for each additional 10 g per day intake of alcohol i.e. for each extra unit/drink of alcohol consumed on a daily basis. Information on alcohol consumption was, however, usually self-reported, describing drinking habits at around the time that the women were interviewed. No information on the pattern of intake, including the type of alcohol consumed and the duration of intake, was collected for this collaboration. There is no strong evidence here to suggest biased reporting of alcohol consumption in case-control studies, since there was no significant difference in results between case–control and cohort studies (increases of 7.4% and 5.0% per 10 g per day, respectively; χ^2_1 for heterogeneity=1.5, P=0.2). However, self-reported information on alcohol consumption is known to underestimate true consumption.[68] Systematic under-reporting of consumption by both cases and controls would result in an overestimation of the relative risk of breast cancer for a given level of alcohol consumption. By contrast, random misclassification among both cases and controls would have the opposite effect, resulting in an underestimation of the relative risk. These two types of measurement error are inevitable, but counter-acting, and it is not possible to estimate their overall effect on the relative risks calculated here. Moreover, the shape of the dose-response relationship could be changed if, for example, heavy drinkers were more likely to under-report intake than moderate drinkers. Taken together, these reporting errors imply that some uncertainty remains about the true quantitative effect of an intake of a fixed amount of alcohol on the risk of developing breast cancer.

The true relationship between alcohol consumption and breast cancer might, perhaps, be more curved than is suggested by the shape of the relationship shown in Figure 1, because of misclassification of alcohol intake, as may also have occurred with cigarette smoking and lung cancer.[71] Any firm conclusion about the risk of breast cancer at low levels of alcohol intake is, however, prohibited by the likelihood of measurement errors, particularly the tendency for underestimation of the amount drunk, and by the possibility that non-drinkers may differ in some relevant, but unmeasured, ways from those who sometimes drink alcohol. Hence, the possibility of a threshold dose of alcohol cannot be reliably assessed from the data in Figure 1.

These results provide no direct evidence about possible mechanisms of carcinogenesis by alcohol on the breast. There is, however, accumulating evidence that regular intakes of moderate amounts of alcohol affect sex hormone levels. For example, the results of a recently published small randomised trial of 51 postmenopausal women suggested that sex hormone levels may be increased after the consumption of 30 g per day alcohol for 8 weeks,[72] levels of consumption that are associated here with a clear excess risk of breast cancer.

With respect to the consumption of tobacco, the main exposure variable examined here was whether or not a woman had ever smoked. No information was collected for this collaboration on the amount smoked or on the age that smoking started or stopped, nor has attention been given to the reported effects of environmental exposure to tobacco,[35,49] as active smoking only has been considered. Although some past smokers may have smoked relatively infrequently, current smokers are likely to have had substantial lifetime exposures to tobacco, particularly in countries where lung cancer rates in women are high. Just over half the ever-smokers included in these analyses were current smokers,

and among them the risk of breast cancer was similar to that in never-smokers (relative risk=0.99 (95% CI, 0.96–1.03)). The findings from case–control studies could, in theory, be biased if women with breast cancer stopped smoking when they first developed symptoms, or if there were differential reporting of smoking by cases and controls. However, the results from cohort studies, where exposure information was collected prospectively, suggest no increase in the risk of breast cancer in ever-smokers or current smokers compared to never-smokers (relative risk=1.00, 95% CI 0.93–1.07, for ever-smokers; and =0.94, 95% CI 0.84–1.05, for current smokers).

Public health implications

If the pattern of breast cancer associated with increasing levels of alcohol consumption estimated here is valid, then about 4% of the breast cancers in women in developed countries may be attributable to alcohol. The consumption of alcohol by most women in developed countries is relatively low, with about two-thirds consuming little or no alcohol each day. For women in developed countries who regularly drink alcohol, the lifetime risk of breast cancer is estimated to increase by about 0.7 per 100 women for each extra unit or drink of alcohol consumed on a daily basis. For example, the cumulative incidence of breast cancer by age 80 years is estimated to increase from 8.8 per 100 women who drink no alcohol to 10.1 or 100 who consume two alcoholic drinks daily and to 11.6 per 100 who consume four drinks daily. This excess risk should be considered in the context of the beneficial effects of alcohol, in moderation, on cardiovascular disease, and its harmful effects on cirrhosis and on cancers of the mouth, larynx, oesophagus and the liver.[73,74]

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APPENDIX II. – References to epidemiological studies of breast cancer and alcohol and tobacco consumption and to reviews of the topic

(This can be viewed on the website www.bjcancer.com)

APPENDIX III. – Results on the relation between current smoking and breast cancer in women who reported drinking no alcohol

(This can be viewed on the website www.bjcancer.com)

APPENDIX IV. – Results on the relation between past smoking and breast cancer in women who reported drinking no alcohol

(This can be viewed on the website www.bjcancer.com)

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ORIGINAL PAPER

Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues

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Abstract
Objective To give an up-to-date assessment of the association of alcohol with female breast cancer, addressing methodological issues and shortfalls in previous overviews.
Methods Meta-analysis of studies (any language) providing original data on incidence of first primary breast cancer and alcohol. Two reviewers independently extracted data. Study quality assessed by objective criteria including degree of control for confounding; funnel plots examined for publication bias; meta-regression techniques to explore heterogeneity. Risks associated with drinking versus not drinking and dose–response not constrained through the origin estimated using random effects methods.
Results Ninety-eight unique studies were included, involving 75,728 and 60,653 cases in drinker versus non-drinker and dose–response analyses, respectively. Findings were robust to study design and analytic approaches in the meta-analyses. For studies judged high quality, controlled for appropriate confounders, excess risk associated with alcohol drinking was 22% (95% CI: 9–37%); each additional 10 g ethanol/day was associated with risk higher by 10% (95% CI: 5–15%). There was no evidence of publication bias. Risk did not differ significantly by beverage type or menopausal status. Estimated population attributable risks were 1.6 and 6.0% in USA and UK, respectively.
Conclusions Taking account of shortcomings in the study base and methodological concerns, we confirm the alcohol–breast cancer association. We compared our results to those of an individual patient data analysis, with similar findings. We conclude that the association between alcohol and breast cancer may be causal.

Keywords Alcohol · Breast cancer · Epidemiology · Meta-analysis

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Introduction

Meta-analysis provides a succinct and statistically powerful summary of data from different studies [1]. However, there are particular challenges when meta-analysis is applied to observational data, as, unlike randomized controlled clinical trials (RCTs), they are prone to confounding and various biases, which might distort the results [2]. We explore here the application of meta-analysis to studies of the association of alcohol and breast cancer with particular attention to issues of confounding and bias in observational data. Our aim was to carry out a more complete assessment of these issues than in previous meta-analyses [3–7] so as

to provide robust quantitative estimates of the alcohol–breast cancer association to guide public health policy. We focus in particular on issues of study quality including treatment of confounders, and on the problems associated with the reporting and analysis of alcohol consumption, with consideration of methods to investigate dose–response and heterogeneity of effect between studies. We compare our results with those of a recent meta-analysis of individual patient data (IPD) [8], which may be less affected by these problems, and assess the extent to which careful application of meta-analysis methods can aid interpretation and inform policy in an area where RCTs are not feasible.

Methods

Studies were identified by searching all relevant databases (Medline, EMBASE, Pascal (BIDS), Science Citation Index (BIDS), Social Sciences Citation Index (BIDS), Index to Scientific and Technical Proceedings (via BIDS), Biological Abstracts (BIOSIS), Biological Sciences, AIDS and Cancer Research Abstracts, Biology Digest, Conference Papers Index, Cochrane Library, NHS National Research Register (NRR), SIGLE (System for Information on Grey Literature), NTIS (National Technical Information Service), TOXLINE) using key words such as breast, neoplasm, and ethanol, and by scanning the references of identified papers. We used a variety of search methods to minimize publication bias, including citation searching, identification of grey literature and searches of conference proceedings. The initial search was kept broad in order to capture all relevant publications.

A study was eligible for inclusion if it (i) gave original data, (ii) assessed incidence (not mortality or prevalence), (iii) considered first primary breast cancer, (iv) was published in any language between 1 January 1966 and 31 December 2003. We identified 298 papers for abstraction of which 187 were excluded because of duplication, inappropriate or missing data, or not reporting original research (i.e., editorial, comment or review), leaving 111 for inclusion in our meta-analysis. These 111 papers related to 98 unique studies.

We used a simple scoring system to assess study quality as follows: 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. Data were abstracted and studies scored independently by two reviewers (JK, SH); any discrepancies were referred to a panel (RO, TJ, PE, ST) for resolution.

To avoid violating independence assumptions, studies were included once only; for the same reason, only one set of controls could be included. We therefore decided, a priori, on the following hierarchy: where a study had been published more than once, odds ratios adjusted for the most appropriate confounders were used in preference; otherwise, the analysis that included the greatest number of participants was used. Where results for more than one control group were reported: community was preferred to hospital controls, and non-cancer to cancer controls.

Studies were categorized as either retrospective (i.e., case–control or retrospective cohort) or prospective (i.e., follow-up studies, including nested case–control studies). None of the cohort studies had more than one set of controls.

Statistical analysis

Definition of non-drinker varied between studies and in some cases included infrequent drinkers (Table 1, studies 8, 15, 16, 22, 30, 68, 71, 72), ex-drinkers (studies 1, 3, 14, 19, 20, 23, 25, 26, 28, 34, 36, 38, 41–43, 51, 52, 54, 57, 59, 60, 62, 64, 77–81, 83, 87–89, 91, 93, 95, 98) or both infrequent and ex-drinkers (studies 4, 10, 13, 37), while in some studies, the term non-drinker was not further defined (studies 2, 5–7, 9, 12, 21, 24, 27, 29, 32, 35, 40, 44, 46, 53, 58, 67, 69, 70, 73, 92, 97, 99). As it was not possible from the published data to reassign individuals to a common definition of non-drinker, the study specific definitions were used, recognizing that this might lead to dilution of effect. Similarly, beer, wine and spirits were classified according to definitions used in each publication. Alcohol consumption was converted to g/day using conversion factors appropriate to each country [9]. As the data on alcohol consumption were presented categorically, we used the midpoint of each consumption band to estimate dose–response, and for the highest consumption band (which was usually open-ended) we assigned a value half the width of the previous interval above the uppermost cut point [5] (we carried out a sensitivity analysis to this choice).

Where estimates of risks were reported for subsets of the study population (e.g., pre/postmenopausal, oestrogen receptor status), we used a Woolfe adjusted method [10] to obtain study-wide risk estimates. We carried out an analysis of drinkers versus non-drinkers with use of random effects methods [11] to combine log odds ratios across studies, using a moment estimator of the between study variance. Where a study gave a dose–response analysis

Table 1 Summary of included studies

	Country	Study ID and date	Control	Analysis	# Cases in most adjusted analysis	# Controls in most adjusted analysis	Confounders in most adjusted analysis
Retrospective studies							
1	Australia	Rohan (1988)	C	E, D	451	451	a, b, c, d, g, h, i, j, k, l, p, practice of breast self-examination
2	Australia	Price (1999)	C	E, D	276	1,846	a
3	Brazil	Gomes (1995)	H	E	144	567	a
4	Canada	Rosenberg (1990)	C	E, D	534	1,044	a, b, d, f, g, h, i, j, k, l, m, p, religion, dietary intake, neighbourhood
5	Canada	Band (2002)	C	E	1,018	1,025	a, d
6	Canada	Cotterchio (2003)	C	E, D	2,509	3,511	
7	Canada	Friedenreich (2001)	C	E	1,233	1,237	d
8	Canada	Lenz (2002)	H	E, D	556	577	a, b, e, g, h, i, j, l, m, o, p, age at oophorectomy, marital status, proxy respondent status
9	Chile	Atalah (2000)	H	E	170	340	a
10	Denmark	Ewertz (1991)	C	E, D	1,361	1,226	a
11	Finland	Mannisto (2000)	C	E, D	301	443	
12	France	Le (1984)	H	E, D	500	945	a, b, d, f, g, j, k, l
13	France	Richardson (1991, 1989)	H	E, D	234	325	a, b, c, d, f, g, j, k, l, m
14	France	Viel (1997)	C	E, D	154	154	a, f, total calorie intake
15	Germany	Kropp (2001)	C	E, D	706	1,381	a, d, e, f, j, l
16	Germany	Nienhaus (2001)	H	E, D	681	651	a, d, j, survey location
17	Greece	Katsouyanni (1994)	C	E, D	798	1,528	a, b, d, f, g, m, total energy intake, place of birth
18	Holland	Van't Veer (1989)	C	E, D	116	161	a, d, f, g, j, l, m, p, region, season, energy percent fat intake
19	Italy	Talamini (1984)	H	E, D	368	373	a, b, c, f, g, h, i, l, m, p, marital status, food intake
20[a]	Italy	Ferraroni (1991, 1993)	H	E, D	210	214	a, b, c, d, f, g, j, l, m
21	Italy	La Vecchia (1989), Soler (1999), La Vecchia (1985)	H	E, D	2,402	2,220	a, b, c, d, f, g, h, i, j, l, p, geographic area, marital status, intake of meat, fats and green vegetables
22	Italy	Ferraroni (1998)	H	E, D	2,425	2,437	a, b, f, g, j, l, m, total energy intake
23	Italy	Toniolo (1989)	C	E, D	250	499	a, d, m, total energy intake
24	Sicily/Italy	Cusimano (1989)	H	E	143	286	a, l
25	Italy	Franceschi (1991)	H	E, D	132	499	a, g, l, meat and vegetable intake
26	Japan	Kato (1989)	H	E	1,740	8,920	a
27	Japan	Hirose (1995), Hirose (2003)	H	E, D	1,036	20,797	a, d
28	Japan	Kikuchi (1990)	C	E	48	48	a
29	Japan	Kato (1992)	H	E	899	899	
30	Korea	Choi (2003)	H	E	346	377	a, j
31	New Zealand	Sneyd (1991)	C	E, D	840	1,782	a, b, f, l, p
32	Nigeria	Adebamowo (1999)	H	E	251	251	
33	Poland	Pawlega (1992)	C	E	122	239	a, d, l, m, p, marital status, no. of persons in household
34	Russia	Zarridze (1991)	C		139	139	a, b, d, g
35	Spain	Viladiu (1996)	C	E, D	330	346	a, c, d, g, j
36	Spain	Martin-Moreno (1993)	C	E, D	762	988	a, b, c, d, g, j, l, m, geographic region, total energy intake
37	Sweden	Ranstam (1995)	C		393	449	
38	Sweden/Norway	Adami (1988)	C	E, D	422	527	a, b, d, f, g, i, j, k, l, p
39	Switzerland	Levi (1996)	H	E, D	230	507	a, c, d, f, g, h, i, j, l, p, marital status
40	Switzerland	Morabia (1996)	C	E, D	150	336	a, b, g, i, j, k, l, m, saturated fat intake
41	UK	Meara (1989)	H	D	998	998	a, b, d, g, i, j, l, m, p
42	UK	Meara (1989)	C	D	118	118	a, b, d, g, i, j, l, m, p
43	UK	Smith (1994)	C	E, D	753	753	a, b, d, e, f, g, i, j, k, p
44	USA	Boice (1995)	C	E, D	521	2,611	a, b, c, d, f, g, j, k
45	USA	Vachon (2001)	C	E	558	8,744	a, p, birth cohort, familial clustering, source of information
46	USA	Dupont (1989)	H	E	113	2,483	a, length of follow-up
47	USA	Byers (1982)	H	E, D	1,297	751	a

Table 1 continued

	Country	Study ID and date	Control	Analysis	# Cases in most adjusted analysis	# Controls in most adjusted analysis	Confounders in most adjusted analysis
48	USA	Harris (1988)	H	E	1,467	10,178	a
49	USA	Harvey (1987)	C	E, D	1,524	1,896	
50	USA	O'Connell (1987)	C	E	275	1,519	a
51	USA	Webster (1983), Chu (1989)	C	E, D	1,206	1,256	a, d, g, j, k, l, m, p, religion
52	USA	Young (1989)	C	E, D	255	358	
53	USA	Nasca (1994, 1990)	C	E, D	1,608	1,609	a, d, g, j, k, o
54	USA	Miller (1989)	H	E	404	421	i
55	USA, Canada, Western Europe	Enger (1999), Longnecker (1995)	C	E, D	1,844	1,817	a, d, q
56	USA	Bowlin (1997)	C	E, D	1,211	1,214	a, b, e, g, j, k, l, p, religion, marital status, ever pregnant
57	USA	Freudenheim (1995)	C	E, D	738	810	a, b, d, g, j, k, l, m, intake of calories, and various nutrients and vitamins
58	USA	Harris (1992)	H	E, D	604	520	a, b, c, d, e, f, g, i, j, p
59	USA	Rossing (1996)	C	E, D	537	489	a, d
60	USA	Longnecker (1995)	C	E, D	6,662	9,163	a, b, f, g, j, k, l, m
61	USA	Brinton (1997), Swanson (1997)	C	E, D	1,579	1,442	a, b, d, f, g, i, j, k, m, o
62	USA	Newcomb (1999)	C	E, D	3,623	3,783	a, d
63	USA	Baumgartner (1999)	C	E, D	688	804	a, b, d, e, f, g, i, j, k, l, m, o, p, physical activity, energy intake, energy adjusted fat intake
64	USA	Kabat (1997)	C	E, D	42	64	a, f, m, o, p, eostrogen metabolite ratio, chronic condition
65	USA	Kinney (2000)	C	E, D	856	784	a, b, f, j, k, l, m, o, p
66[c]	USA	Zheng (2003)	H	E, D	317	334	a, d, e, g, j, m
67	USA	Claus (2001)	C	E	959	986	a, b, c, d, f, g, h, i, j, k, l, m, o, p, history of at least one screening mammogram one year before interview
68	USA	Wu (2003)	C	E	490	591	
69	USA	Zhu (2003)	C	E, D	288	291	a, b, d, f, g, h, j, k, l, m, p, employment, marital status, number of people in household, religion, use of electric blanket/mattress pad, physical activity, on a diet to lose weight, number of miscarriages, having an infertility test, intake of vitamins, total energy intake
70	USA	Gammon (2002)	C	E	1,508	1,556	a
71	USA	Li (2003)	C	E, D	967	998	a, j, m
72	USA	Wrensch (2003)	C	E, D	285	286	a, b, d, e, f, h, i, j, k, l, m, p, religion, number of mammograms, previous radiation treatment
73	USA	Xiong (2001)	C	E	100	105	
74	USA/ Canada/Israel	Rosenberg (1982)	H	E	1,146	2,694	a, c, d, f, g, j, k, l, n, o, religion, geographic area, year of interview, number of previous hospital admissions
75	Uruguay	Ronco (1999)	H	E	400	405	
76	[b]	Royo-Bordonada (1997)	C	E, D	315	364	a, b, c, d, f, g, h, j, k, m, p
77	Combined analysis	Howe (1991)	C	E, D	1,573	1,974	a, d
Prospective studies							
78	Canada	Friedenreich (1993), Rohan (2000)		E, D	1,336	5,238	a, b, d, f, j, practice of breast self-examination, study center, energy intake, study allocation
79	Denmark	Hoyer (1992)		D	51	5,156	
80	Denmark	Tjonneland (2003)	C	E, D	416	23,533	a, f, g, h, k, l, m
81	Holland	van den Brandt (1995)		E, D	422	1,579	a, b, c, d, f, g, i, j, k, l, m, p, energy intake
82	Sweden	Holmberg (1995)		E, D	276	452	a, f, g, j, l, m
83	Sweden	Lahmann (2003)	C	E, D	246	11,913	
84	USA	Zhang (1999)		E, D	221	2,543	a, c, d, f, g, h, l, m, p, physical activity index
85	USA	Zhang (1999)		E, D	66	2,218	a, b, c, d, f, h, l, m, p, physical activity index

Table 1 continued

Country	Study ID and date	Control	Analysis	# Cases in most adjusted analysis	# Controls in most adjusted analysis	Confounders in most adjusted analysis
86 USA	Simon (1991)		E, D	87	1,827	a, b, f, g, j, l, m, p, subscapular and triceps skin folds
87 USA	Hiatt (1984)		E, D	838	87,570	a
88 USA	Schatzkin (1987)		E, D	121	7,067	a, b, d, f, g, j, l, m, dietary fat
89 USA	Barrett-Connor (1993)		E	15	575	
90 USA	Hiatt (1988)		D	287	58,044	a, m, o, p
91 USA	Zhang (1999), Willett (1987), Chen (2002)		E, D	3,483	85,335	a, b, c, d, f, g, h, j, k, m, length of follow-up, total energy intake
92 USA	Graham (1992)		D	367	3,670	a, b, d, f, g, h, i, j, k, l, m, p, fat, fibre and energy intake
93 USA	Cerhan (1998)		E	46	1,760	
94 USA	Lucas (1998)		E, D	121	7,894	a, b, c, d, f, g, h, j, k, m, p, physical activity
95 USA	Potter (1995), Gapstur (1992)		E, D	939	36,166	a, b, f, g, i, j, m, q, type of menopause, history of bilateral oophorectomy
96 USA	Garland (1999)		E, D	435	116,236	a, b, d, f, g, j, k, m
97 USA	Feigelson (2003)	C	E, D	1,303	65,258	a, b, c, f, g, h, j, k, l, m, o, dietary folate, methionine, multivitamin use, mammographic history, physical activity, adult weight gain, energy intake
98 USA	Horn-Ross (2002)	C	E, D	681	104,454	a, b, f, g, j, o, daily caloric intake, physical activity
99 Western Europe	Clavel-Chapelon (2002)	C	E, D	2,758	276,473	a, b, f, g, l, m, p, energy intake, follow-up time
100 Combined analysis	Smith-Warner (1989)					a, b, d, f, g, h, i, j, k, l, m, p, fat, fibre and energy intake

[a] There is a small overlap of cases between this study and study 21, it is therefore only used in a sensitivity anlaysis

[b] From 5 countries—Germany, Switzerland, Northern Ireland, Holland, Spain

[c] Overlap of cases with 67, used in a sensitivity analysis for "ever never" and in the main analysis for dose–response

H, case–control study with hospital controls; C, case–control study with community controls; E, "ever" versus "never" drinkers analysis; D, dose–response analysis

Key to confounders: a, age; b, age at menarche; c, age at menopause; d, menopausal status; e, breast feeding; f, parity; g, age at first birth; h, HRT use; i, oral contraceptive use; j, family history of breast cancer; k, history of biopsy for benign breast disease; l, socio-economic status; m, BMI; n, obesity; o, ethnicity; p, smoking status; q, oestrogen receptor status

A list of references referred to in this table are available from the authors on request

only, we calculated a crude odds ratio of drinkers versus non-drinkers using the number of cases and controls in each consumption band. This was not possible for eight studies where either data on number of cases and controls were not given (Table 1, studies 41, 42, 79, 90, 92) or data could not otherwise be pooled (studies 20, 34, 37), so these studies were excluded from the drinkers versus non-drinkers analysis.

Initial exploration of the dose–response data using the "pool-first" method [12], which pools study data before trend analysis, indicated a monotonic increasing function relating alcohol consumption with breast cancer risk; therefore we assumed that the logarithm of the odds ratio varied linearly with alcohol consumption. We also tested for a quadratic association. We calculated dose–response slopes (among drinkers) for each study with available data by use of log linear regression and a variable intercept; that is, we excluded non-drinkers and hence did not constrain the curve to go through the origin. We also compared results with a model that was constrained to go through the origin (zero intercept model). Finally we carried out a meta-analysis of dose–response slopes using random effects methods [11].

We carried out a sensitivity analysis to assess how differing quality criteria (via the simple scoring system) and control for confounding affected the size of the risk estimate, giving seven separate analyses for each question of interest. We examined possible heterogeneity in results across studies using the Q statistic [10]. Meta-regression with random effects [13] was used to explore heterogeneity. Characteristics of the studies examined for heterogeneity were as follows: whether the data were collected before or after disease onset; for case–control studies whether the controls were hospital or community based; pre or postmenopausal; and nationality of the study population (USA or Canada/Europe/other).

Estimates of population attributable risks [14] for the USA and UK (calculated as a weighted average of that in

England, Scotland, Wales and Northern Ireland) were obtained from surveys of drinking habits among women stratified by age [15, 16], by use of age-specific cancer registration data for the USA [17] and UK [18], and assuming 12 g of ethanol in an "average" drink in the USA [9] and 8 g in a unit of alcohol in the UK [19]. We used percentages of drinkers in each age group (and categories of amounts consumed). In the USA, these data were available for five age groups and five drinking categories (no drinks in the past year, 1–11 drinks in the past year, ≤3 drinks per week, 3–7 drinks per week, >7 drinks per week) [16]. In the UK, there were seven age groups and five drinking categories (<1, 1–7, 7–14, 14–21, >21 units per week) [15]. The percentage of drinkers (% heavy drinkers, defined as the highest category of alcohol drinking in each country) by age were, in the USA: 18–24 years 56% (4%), 25–44 years 66% (4%), 45–64 years 56% (4%), 65–74 years 41% (3%), ≥75 years 29% (2%) [16]. In England these percentages were: 15–24 years 79% (17%), 25–34 years 77% (11%), 35–44 years 77% (10%), 45–54 years 74% (10%), 55–64 years 66% (6%), 65–74 years 53% (4%), ≥75 years 46% (3%) [15]. (Similar data were available for Scotland [15]; we assumed drinking habits in Wales and Northern Ireland to be the same as in England.) The calculation uses results from the dose–response analysis. All analyses were carried out using Splus.

Results

Table 1 gives case and control numbers (most completely adjusted analyses) and brief details of all included studies, by country and dates of study, for both retrospective and prospective designs.

Drinkers versus non-drinkers

Figure 1 shows crude odds ratios with 95% confidence intervals for the 89 studies included in the analysis of drinkers versus non-drinkers. Studies are ranked according to precision. Overall 29 studies had estimated odds ratio <1 and 60 studies ≥1, with combined estimate of 1.11 (95% CI: 1.06–1.17). Table 2 gives results, including Q-statistics, which give a measure of heterogeneity, of the meta-analysis for seven separate analyses according to degree of control for confounding and criteria for study quality (scores of 1, 2 or 3, see Methods). This sensitivity analysis shows effects of study quality and differing control for confounding on size of the estimate. The results are also shown in Fig. 2. The estimates ranged from 1.11 (95% CI: 1.06–1.17) (least adjusted estimate including all studies, Fig. 2a) to 1.22 (95% CI: 1.09–1.37) (multivariate adjustment for confounders in the 19 studies with score 3, Fig. 2g). We analysed data separately for drinkers versus non-drinkers of beer (30 studies), wine (32 studies) and spirits (31 studies) where relevant data were available; 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.

Dose–response

Figure 3 is a scatter plot of the log odds ratios of risk of breast cancer associated with drinking alcohol. Also shown on the plot are the linear and quadratic fits to the data using the "pool-first" method. Data are for the least adjusted odds ratios from all studies that provided number of cases and controls per drinking category (these data are required for the "pool-first" trend calculation). The quadratic fit is not significantly better than the linear fit at the 5% level.

Table 2 and Fig. 4 give results of the meta-analysis of dose–response and show, amongst drinkers, the higher risk associated with drinking an extra 10 g of ethanol a day. Again, results for the seven analyses are shown separately according to degree of control for confounding and study quality. The combined estimate of excess risk ranged from 10% (95% CI: 5, 15%) (multivariate adjustment for confounders in studies with score 3, Fig. 3g) to 13% (95% CI: 9, 17%) (least adjusted, studies with score 2 or 3, Fig. 4b). From the studies judged of high quality with control for appropriate confounders (Fig. 4g), and assuming in the USA

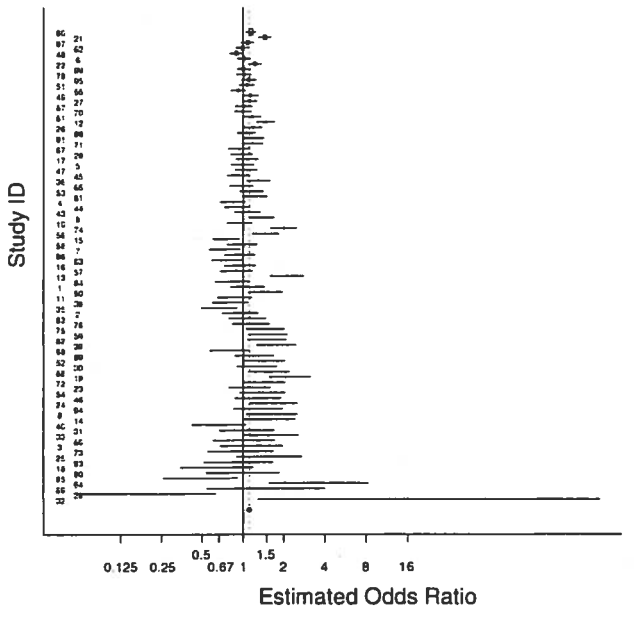

Fig. 1 Individual study estimates of crude odds ratios (log scale) of the risk of breast cancer associated with drinkers versus non-drinkers and 95% confidence intervals. The estimates are ranked top to bottom by precision. Area of box showing study point estimate is proportional to precision. Study ID (Table 1) is given down the left-hand side. The diamond at the bottom of the plot denotes the random effects estimate of the combined result

Table 2 Results of meta-analysis

Model	Drinkers versus non-drinkers			Dose–response		
	OR (95% CI)	# Studies	Q-Statistic	Percent excess risk (95% CI) per 10 g ethanol per day	# Studies	Q-Statistic
a	1.11 (1.06, 1.17)	89	319	12 (9, 15)	71	124
b	1.12 (1.06, 1.18)	61	214	13 (9, 17)	54	98
c	1.17 (1.09, 1.26)	35	120	11 (7, 15)	41	57
d	1.17 (1.09, 1.26)	28	76	12 (8, 17)	34	52
e	1.16 (1.10, 1.24)	54	165	11 (7, 14)	63	102
f	1.17 (1.10, 1.24)	42	106	12 (8, 16)	51	91
g	1.22 (1.09, 1.37)	19	54	10 (5, 15)	33	56

a, Least adjusted odds ratios from all studies

b, Least adjusted odds ratios, studies with score 2 or 3

c, At least age adjusted odds ratios from all studies

d, At least age adjusted odds ratios, studies with score 2 or 3

e, Multivariate adjusted odds ratios from all studies

f, Multivariate adjusted odds ratios, studies with score 2 or 3

g, Multivariate adjusted odds ratios, studies with score 3

an "average" drink contains 12 g of ethanol [9], a woman drinking an average of two drinks per day compared to a woman who drinks on average one drink per day has a risk estimated to be 12% (95% CI: 7–19%) higher. For the UK, where an "average" drink contains 9.5 g ethanol [9], the estimated risk is 10% (95% CI: 5–15%) higher for two drinks per day compared with one. Figure 5 shows the slopes fitted to each study, using the most completely adjusted analyses for studies that scored 3, for the variable and zero intercept models for dose–response.

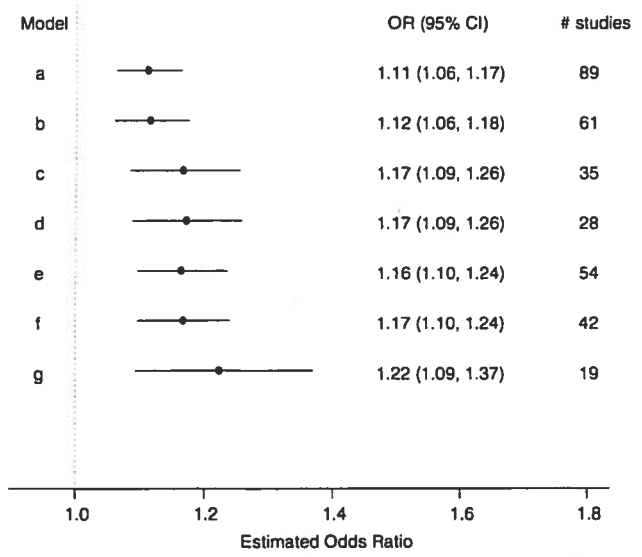

Fig. 2 Estimates of the combined odds ratio and 95% confidence interval for drinkers versus non-drinkers. Each line corresponds to an analysis with different inclusion criteria according to study quality (see Methods) and degree of confounding. Odds ratios combined in each analysis are (**a**) least adjusted odds ratios from all studies, (**b**) least adjusted odds ratios, studies with score 2 or 3, (**c**) at least age adjusted odds ratios from all studies, (**d**) at least age adjusted odds ratios, studies with score 2 or 3, (**e**) multivariate adjusted odds ratios from all studies, (**f**) multivariate adjusted odds ratios, studies with score 2 or 3, (**g**) multivariate adjusted odds ratios, studies with score 3

Heterogeneity

All analyses showed significant heterogeneity ($P<0.05$) across studies in size of association between alcohol consumption and risk of breast cancer (Q-statistics, Table 2). Of the various factors entered into meta-regression analyses to explore the heterogeneity, in the analyses 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 (for example, odds ratios of 1.39 (95% CI: 1.21–1.60) and 1.11 (95% CI: 1.02–1.21), respectively based on multivariate odds ratios from studies scoring 2 or 3); for the dose–response analyses, there were no significant differences between analyses based on hospital and community controls (for example, odds ratios of 7% (95% CI: 2–12%) and 13% (95% CI: 10–17%) per 10 g ethanol, respectively, based on studies scoring 2 or 3). None of the other variables examined in meta-regression significantly reduced the heterogeneity across studies.

Sensitivity analysis

We checked the sensitivity of our results to the dose–response calculation; sensitivity to 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 by using binomial logistic

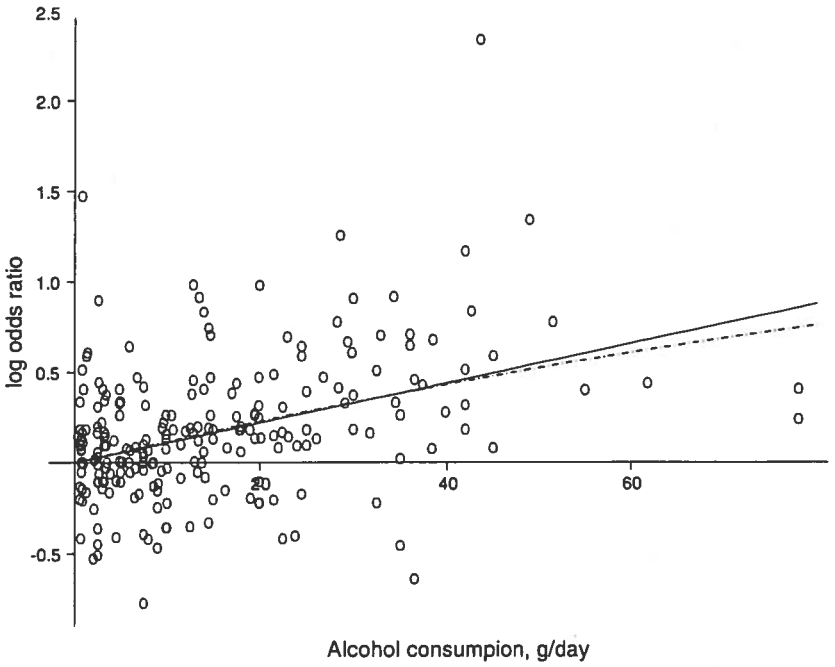

Fig. 3 Scatter plot of the log odds ratios of risk of breast cancer associated with alcohol consumption. Solid and dashed lines show the linear and quadratic fits, respectively using the "pool-first" method. Non-drinkers are included in the model fits

rather than log linear regression to estimate the dose–response curve at the study level. We also checked sensitivity to alternative choice of controls where these were reported. None of these appreciably altered the results. As can be seen in Fig. 1 there was no indication that smaller studies (indicated by large confidence intervals) were more positive. Formal funnel plots [20] also did not indicate any evidence for publication bias, including for subset analyses.

Population attributable risk

We estimated the population attributable risk among drinkers of alcohol in the USA and UK to be 1.6 and 6.0%, respectively. We assessed the sensitivity of these estimates by recalculating them based on the lower and upper 95% confidence interval for the estimated slope; with these sensitivity limits, our population attributable risk estimate ranged from 0.9 to 2.4% in USA and 3.2 to 8.8% in the UK.

Discussion

This is the largest and most comprehensive meta-analysis to date of the relationship of alcohol to breast cancer, and in our view provides a sound basis for guiding public health policy in this area. We included 98 studies and some 20,000 more cases than the largest of the previous meta-analyses [8]. Compared with previous meta-analyses, all of which reported a positive association of alcohol to breast cancer [3–8], we included non-English publications, an assessment of the association of drinking versus not-drinking alcohol, extensive sensitivity analysis to quality of included studies and adjustments for confounders, assessment of the dose–response relationship among drinkers (i.e., excluding non-drinkers), and exploration of risk by type of alcoholic beverage. We also include an estimate of population attributable risk. Based on these extensive analyses, previous estimates of the positive association of alcohol to breast cancer are shown to be robust.

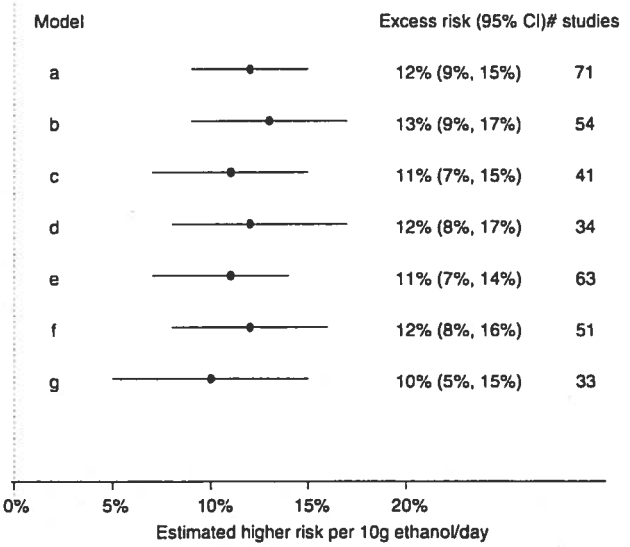

Fig. 4 Estimates of the increase in risk of breast cancer amongst drinkers per 10 g ethanol/day. Each line corresponds to an analysis with different inclusion criteria according to study quality (see Methods) and degree of confounding. (a)–(g) as in Fig. 2

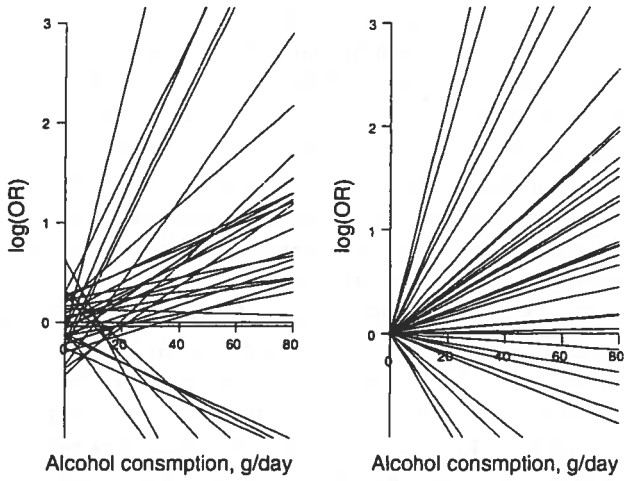

Fig. 5 Comparison of variable and zero intercept models (dose–response). Fitted slopes for most adjusted odds ratios from studies scoring 3. Left figure shows the slopes fitted using the variable intercept model (non-drinkers excluded), right figure shows the slopes fitted using the zero intercept model (non-drinkers included)

Methodological considerations

Meta-analysis of observational studies presents challenging methodological issues involving different study designs (case–control and cohort), and variation in the quality of studies in terms of response rate, missing data, exposure assessment, control for confounding, and choice of controls in the case–control studies. A potential limitation of our study, in common with other meta-analyses of observational studies (compared with meta-analyses of RCTs), is the issue of bias. We made every effort to identify and deal with sources of bias in the published data. We carried out a sensitivity analysis based on pre-defined quality criteria and control for confounding. Our scoring system was simple and objective, as an over-complicated system might introduce subjectivity and bias into the analysis. Inclusion of quality scores as covariates or weights in a meta-analysis will lead to bias [21]. However, our score criteria were selected to identify studies with potential biases due to design issues or confounding, so that such studies could be excluded in the sensitivity analyses (even though this will result in increased variance due to smaller sample size). We did not include the scores as part of the regression analyses, or as weights.

Another possible limitation of meta-analysis of published data is the issue of confounding as studies differ in their definitions of the various confounding variables, and the confounders included vary between studies. While our definition of "sufficient control for confounding" was broad enough to encompass a range of potential confounders, it was still able to identify a subset of studies with at least a similar approach to the treatment of confounding. We further explored the effects of confounding by comparing analyses of least adjustment, at least age adjustment, and multivariate adjustment. Although results varied, positive and significant associations were found in all analyses. Pooling multivariate adjusted results from studies of adequate design with sufficient control for confounding, is likely to be the optimal analysis in terms of accounting for bias, assuming the studies are sufficiently homogeneous. If the studies are too heterogeneous, then it may be that a pooled risk estimate is inappropriate.

Consideration of study design is important. Case–control studies are more prone to bias than cohort studies, in particular with respect to exposure assessment and recall bias. Among case–control studies, controls are either hospital or community-based. Ideally controls should be selected independently of exposure, but hospital patients may not be representative of the exposure distribution in the source population (though authors using hospital-based controls generally stated that they attempted to exclude subjects with diseases related to alcohol consumption). We used meta-regression to explore heterogeneity due to these factors. We did not find a significant difference between risks estimated using case–control and cohort studies. However, we did find that among case–control studies, risk estimated using hospital-based controls was significantly higher than that using community-based controls for the drinker versus non-drinker analysis—though a significant positive association was still found after exclusion of studies using hospital-based controls—but not for the dose–response analysis. We also explored for heterogeneity according to pre/postmenopausal status and country. Again using meta-regression, we did not find any significant differences. It is reassuring to note that in every analysis carried out there was a significant positive association, and therefore the findings are consistent over a range of scenarios.

Bias can be introduced into a meta-analysis by including studies favouring a positive result (publication bias) or by abstracting incorrect data. To ensure that publication bias was minimized we undertook an extensive literature search that was not restricted to publications in English and included searching grey literature; we found no evidence of publication bias in our analysis. Two researchers independently abstracted all data and resolved any discrepancies by consensus to reduce observer bias.

Misclassification of exposure is another source of bias. There is potential for bias if light, infrequent or ex-drinkers are classified as non-drinkers, as was the case in many studies analysed. However, this bias is not present in our analysis of dose–response since non-drinkers were excluded (affecting the vertical placement of the slope but not its estimate). In addition, people may under-report the amount of alcohol consumed, especially heavy drinkers [22]. In an analysis of dose–response such a bias may

exaggerate the slope, but should not generate a non-zero slope where there is no association.

An important methodological feature was our use of a variable intercept model when assessing the dose–response relationship. There are several reasons for doing this: (i) it does not assume that any linear dose–response relationship passes through the origin. For example, at small doses the relationship may be non-linear e.g., with lower risks than for zero exposure. Thus a variable intercept model allows for departure from linearity around the origin, while still allowing a linear relationship with doses away from zero; (ii) as noted, the reference group (non-drinkers) may be contaminated to some extent by the inclusion of ex-drinkers or women who drink only occasionally, which makes it more difficult to estimate the effect around the origin; (iii) to take account of systematic differences (other than alcohol intake) between women who drink and those who abstain from alcohol, as this may induce an "apparent" effect associated with drinking. (iv) If there were a threshold effect at a low dose of alcohol, a zero intercept model would induce a dose–response relationship whereas a variable intercept model would not. By anchoring all slopes at the same point, the zero intercept model forces the dose–response slopes of each study (i.e., the observed relationship) to differ, whereas the variable intercept model is more accepting of a common relationship, seen as parallel slopes. Therefore, with respect to the estimated dose–response slope, the zero intercept model forces more heterogeneity between the studies.

Our estimate of population attributable risk in the UK was higher than in the USA, reflecting different drinking habits in the two countries; the USA estimate was similar to that reported previously [23].

Comparison with an individual patient data analysis (IPD)

An individual patient data analysis, where source data are obtained from the investigators rather than relying on published accounts, should give a more comprehensive assessment of risk than a standard meta-analysis, particularly with respect to exposure classification and dealing with confounders. However, IPDs are not widely carried out because they are expensive and time-consuming. Both a standard meta-analysis and an IPD require data from all relevant studies, both published and unpublished, to avoid bias. In practice, sample data are unlikely to be available from all investigators, and thus, unlike a standard meta-analysis, an IPD analysis may not include all the published studies. On the other hand, they are likely to include unpublished data, and inclusion of these data in an IPD analysis may give an advantage over standard meta-analysis.

Not all of the data and analytical problems associated with meta-analysis can be solved by carrying out an individual patient data analysis. For example, the definition of a non-drinker was not consistent across studies, and sometimes included infrequent or ex-drinkers, often reflecting data captured in the original study questionnaire. Study design issues such as low response rate or selection of controls are also problems that cannot be solved by an individual patient data analysis.

The Oxford collaborative study [8] is the largest of the previous meta-analyses and included re-analysis of individual data. They were able to include data from 19 unpublished studies, which were therefore not included in our analysis. However, they did not include data from 67 studies, involving over 40,000 cases, which have been included in the meta-analysis reported here. The Oxford study did not account for quality of included studies and included non-drinkers in their estimate of dose–response. Despite these differences, results are comparable with ours, with the Oxford study finding a 7.1% higher risk for each additional 10 g ethanol per day compared with our estimate of 10% (95% CI: 5–15%) based on studies judged of high quality with appropriate control for confounding.

Biological plausibility

Given the positive association of alcohol intake to breast cancer is robust and not readily explained by bias, confounding or heterogeneity, a causal interpretation needs to be considered. What then, might be the biological mechanism? Whilst alcohol may be directly carcinogenic to the breast, it is more likely to act indirectly through one or more mechanisms. For example, it may influence the metabolism of mammary carcinogens through induction or inhibition of P450 enzymes [24, 25]. However, direct evidence for such involvement in breast cancer is lacking [26–28].

Several studies [29–31] have reported that alcohol consumption is associated with an increased amount of mammographically dense tissue in the breast. It has been found that mammographic density is positively associated with plasma insulin-like growth factor I (IGF-I) levels and inversely associated with plasma IGF binding protein 3 (IGFBP-3) in premenopausal women [32]. Yu and Berkel [33] reported that moderate consumption of alcohol increases the production of IGFs by the liver and suggested that elevated circulating levels of IGFs may stimulate or promote the development and/or growth of breast cancer.

As breast cancer has a hormonal aetiology [34], any effects of alcohol on the endogenous hormonal milieu in women could provide a potential mechanism for carcinogenesis. Alcohol increases endogenous oestrogen levels in

pre- and postmenopausal women [35, 36], possibly via an increased rate of aromatization of testosterone or decreased rate of oxidation of oestradiol to oestrone [37], and elevated levels of oestrone sulphate, a long-term indicator of oestrogen levels, have been demonstrated in women who regularly consume alcohol [38].

There were insufficient data in our study to investigate possible interactions with hormone replacement therapy (HRT) and with oestrogen receptor/progesterone receptor (ER/PR) status of the tumour. More studies are needed to assess such possibilities.

Summary

To summarize, we have shown that 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. We have compared our results with those of an analysis of individual patient data, with similar findings from the two approaches. Although the excess risk associated with drinking alcohol is relatively small compared with the major risk factors for breast cancer [39], it is one of the few modifiable risk factors associated with breast cancer. Given the high prevalence of drinking, even a small risk linking breast cancer with alcohol, if causal, has serious public health implications in terms of the number of breast cancer cases attributable to drinking alcohol.

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Breast Cancer 2010 Report

Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer

Continuous Update Project

CUP

WORLD CANCER RESEARCH FUND GLOBAL NETWORK

OUR VISION

The World Cancer Research Fund global network helps people make choices that reduce their chances of developing cancer.

OUR HERITAGE

We were the first cancer charity:

- To create awareness of the relationship between diet and cancer risk
- To focus funding on research into diet and cancer prevention
- To consolidate and interpret global research to create a practical message on cancer prevention

OUR MISSION

Today the World Cancer Research Fund global network continues:

- Funding research on the relationship of nutrition, physical activity and weight management to cancer risk
- Interpreting the accumulated scientific literature in the field
- Educating people about choices they can make to reduce their chances of developing cancer

THE WCRF GLOBAL NETWORK

The World Cancer Research Fund (WCRF) global network comprises WCRF International, which operates as the umbrella association for the global network's four charitable organisations: The American Institute for Cancer Research (AICR); World Cancer Research Fund (WCRF UK); World Cancer Research Fund Netherlands (WCRF NL); World Cancer Research Fund Hong Kong (WCRF HK).

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This Report provides an updated version of section 7.10 Breast Cancer from the Second Expert Report: Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. This section has been updated with the latest information from the 2008 Continuous Update Project Breast Cancer SLR prepared by a team at Imperial College London, UK (see acknowledgements). For further details on the epidemiological evidence please see the full 2008 Continuous Update Project Breast Cancer SLR (Second Expert Report). For further details on mechanisms please see the Second Expert Report.

The First and Second Expert Reports represent the most extensive analysis of the existing science on the subject to date. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project, in collaboration with Imperial College London. The Continuous Update Project builds upon the work conducted for the Second Expert Report and began by merging all the databases from the different cancer sites into an upgraded database.

The Continuous Update Project provides the scientific community with a comprehensive and up to date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It also provides an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's cancer prevention recommendations based on the 2007 Expert Report.

In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the Continuous Update Project systematically reviews the science. WCRF/AICR has convened a panel of experts (the Continuous Update Project Panel (see acknowledgements) consisting of leading scientists in the field of diet, physical activity, obesity and cancer who consider the evidence produced by the systematic literature reviews and meta-analyses, and consider the results and draw conclusions before making recommendations.

The updates to the SLRs are being conducted by a team of scientists at Imperial College London in liaison with the SLR centres where possible.

Instead of periodically repeating the extensive task of conducting multiple systematic literature reviews that cover a long period of time, the continuous review process is based on a live system of scientific data that is updated on an ongoing basis from which, at any point in time, the most current review and meta-analysis of scientific data can be performed.

Periodically WCRF/AICR will produce reports which will outline the scientific developments in the field of diet, physical activity, obesity and cancer. The reports may also include updates to the WCRF/AICR recommendations.

The updated recommendations will be used by the WCRF/AICR education and media relation departments to inform the general public both of the benefits of a healthy lifestyle and of the developments in science that underpin these recommendations.

New information in this report

Section 1. Updated with recent mortality and survival data.

Section 2. Updated section on family history

Section 3. No update

Section 4. No update

Section 5. A new section briefly describing the methodology of the Continuous Update Project

Section 6. Evidence has been updated based on the 2008 Continuous Update Project Breast Cancer SLR and judgements from the Continuous Update Project Panel

Section 7. Provides a comparison with the Second Expert Report.

Since publication of this report in 2011, some changes have been made to the design and formatting, but no changes have been made to the content of the report or Panel conclusions. Please note, however, that the Second Expert Report matrix in this report has been replaced with the Continuous Update Project Matrix (on page 3).

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (PREMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks
Probable	Body fatness	Adult attained height[1] Greater birth weight
Limited - suggestive	Physical activity[2]	
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; total fat; folate; vitamin D; calcium; glycaemic index; dietary patterns; adult weight gain; abdominal fatness	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
2 Physical activity of all types: occupational, household, transport and recreational.

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (POSTMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks Body fatness Adult attained height[1]
Probable	Physical activity[2]	Abdominal fatness Adult weight gain
Limited - suggestive		Total fat
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; folate; vitamin D; calcium; selenium; glycaemic index; dietary patterns; birth weight; energy intake	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
2 Physical activity of all types: occupational, household, transport and recreational.

Cancer of the breast is the most common cancer in women worldwide. Around 1.1 million cases were recorded in 2004.

Observed rates of this cancer increase with industrialisation and urbanisation, and also with facilities for early detection. It remains much more common in high-income countries but is now increasing rapidly in middle- and low-income countries, including within Africa, much of Asia, and Latin America. Breast cancer is fatal in under half of all cases and is the leading cause of death from cancer in women (fifth for men and women combined), accounting for 16 per cent of all cancer deaths worldwide in 2004.

Breast cancer is hormone related, and the factors that modify risk of this cancer when diagnosed premenopausally and when diagnosed postmenopausally (much more common) are not the same.

The Continuous Update Project Panel judges as follows:
The evidence that lactation protects against breast cancer at all ages is convincing.

Physical activity probably protects against breast cancer postmenopause, and there is limited evidence suggesting that it protects against this cancer diagnosed premenopause. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing, and these are probably also a cause of breast cancer diagnosed premenopause.

The factors that lead to greater birth weight, or its consequences, are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably also a cause. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

Life events that protect against breast cancer include late menarche, early pregnancy, bearing children, and early menopause, all of which have the effect of reducing the number of menstrual cycles, and therefore lifetime exposure to oestrogen. The reverse also applies.

See chapter 8 of the Second Expert Report for evidence and judgements on factors that modify risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable" show that lactation protects against breast cancer; that alcoholic drinks are a cause of this cancer; that the factors that lead to a greater adult attained height, or its consequences, are a cause of postmenopausal and probably also premenopausal breast cancer; that factors leading to greater birth weight, or its consequences, are

probably a cause of premenopausal breast cancer; and that abdominal body fatness and adult weight gain are probably a cause of postmenopausal breast cancer. Body fatness is a cause of postmenopausal breast cancer but probably protects against premenopausal breast cancer.

Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts, and connective tissue. Breast tissue develops in response to hormones such as oestrogens, progesterone, insulin and growth factors. The main periods of development are during puberty, pregnancy, and lactation. The glandular tissue atrophies after menopause.

Breast cancers are almost all carcinomas of the epithelial cells lining the ducts (the channels in the breast that carry milk to the nipple).[1] Premenopausal and postmenopausal breast cancers are considered separately in this Report. Although rare (less than 1 per cent of cases [2]), breast cancer can occur in men, but it is not included here.

1. Trends, incidence, and survival

Breast cancer is the most common cancer in women in high-, middle- and low-income countries.[3] Age-adjusted rates of breast cancer in women are increasing in most countries, particularly in areas where the incidence had previously been low, such as Japan, China and south-eastern and eastern Europe.[4, 5]

This is predominately a disease of high-income countries where overall rates are nearly three times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from 75-100 per 100 000 women in North America, northern Europe, and Australia, to less than 20 per 100 000 in parts of Africa and Asia. [6] In the USA, rates are higher among white women than those from other ethnic groups, although mortality is highest in black women.[7]

Overall risk doubles each decade until the menopause, when the increase slows down or remains stable. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk assume the rate in the host country within one or two generations. This shows that environmental factors are important in the progression of the disease.[8]

Breast cancers can often be detected at a relatively early stage. In countries that provide or advocate screening, most of these cancers are diagnosed when the disease is still at a localised stage.[9] Survival rates range from 90 to less than 50 per cent, depending on the characteristics of the tumour, its size and spread, and the availability of treatment.[10] Average 5-year survival rates are more than 80% in North America, Sweden, Japan, Finland and Australia compared with less than 60 per cent in Brazil and Slovakia and less than 40 per cent in Algeria.[11] The low survival rate in middle- and low-income countries can be explained mainly by a lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by a lack of adequate diagnosis and treatment facilities. Breast cancer accounts for nearly 23 per cent of all cancer incidence in women and 16 per cent of all cancer deaths (all sites except for skin (non-melanoma) and in women only). [3, 6] Breast cancer is the ninth most common cause of death in high income countries and around 69% of all breast cancer deaths occur in middle- and low-income countries.[3] Mortality rates have remained fairly stable between 1960 and 1990 in most of Europe and the Americas; and

have since showed a decline, which has reached 25-30% in northern Europe.[12] See box 1.

Box 1 cancer incidence and survival
The cancer incidence rates and figures given in this Report are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries; regions of some countries have few or no records; records in countries suffering war or other disruption are bound to be incomplete; and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is higher than the figures given here. The cancer survival rates given in this chapter and elsewhere are usually overall global averages. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer and well established treatment facilities. Survival also is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some internal cancers are often evident only at a late stage, which accounts for relatively low survival rates. In this context, 'survival' means that the person with diagnosed cancer has not died 5 years after diagnosis.

2. Pathogenesis

Breast tissue, as well as hormones and hormone-receptor status, varies at different stages of life. It is therefore possible that individual risk factors will have different effects at different life stages (see 6. Evidence and Judgements). Early menarche, late menopause, not bearing children, and late (over 30) first pregnancy all increase breast cancer risk.[8, 13] The age when breasts develop, and menopause, are both influenced by nutrition, with overnutrition leading to early puberty and late menopause; undernutrition delays puberty and advances menopause (see chapter 6.2 Second Expert Report).

Hormones play an important role in breast cancer progression because they modulate the structure and growth of epithelial tumour cells.[10] Different cancers vary in hormone sensitivity. Many breast cancers also produce hormones, such as growth factors, that act locally, and these can both stimulate and inhibit the tumour's growth.[14, 15]

Family history of breast cancer is associated with a 2-3 fold higher risk of the disease. Some mutations, particularly in BRCA1, BRAC2 and p53 result in a very high risk of breast cancer. These mutations are rare and account for only 2 to 5 per cent of total cases.[16] In addition, growth factor receptor genes, as well as some oncogenes, are overexpressed in many breast cancers.[10] (Also see box 2.2. chapter 2, Second Expert Report).

3. Other established causes

3.1 General

This section lists factors outside the scope of this Report, identified as established causes of cancer by the World Health Organization International Agency for Research on Cancer, and other authoritative bodies. These factors are listed in Chapter 2.4 of the Second Expert Report: tobacco use; infectious agents; radiation; industrial chemicals; and some medications. Other diseases may also increase the risk of cancer. In the same way, life events that modify the risk of cancer – causative and protective – are also included.

'Established' effectively means 'beyond reasonable doubt' – roughly the equivalent of the judgement of 'convincing' used in this Report. Occasionally, authorative findings that perhaps fall short of 'established' are also included here.

Where possible, a note of interactive or multiplicative effects with food, nutrition, and the other factors covered by this Report is added, as is any indication of scale or relative importance. The factors here are almost all causative, whereas much of the evidence on food, nutrition, physical activity, and related factors shows or suggests protection against cancer.

3.2 Specific

Life events. Lifetime exposure to oestrogen, influenced by early menarche, late natural menopause, not bearing children, and late (over 30) first pregnancy all increase the risk of, and may be seen as causes of, breast cancer.[8, 13] The reverse also applies: late menarche, early menopause, bearing children, and early pregnancy all reduce the risk of, and may be seen as protective against breast cancer. Age of breast development and menopause are influenced by nutrition, with high-energy diets promoting earlier puberty and late menopause, and low-energy diets delaying puberty and advancing menopause.

Radiation. Ionising radiation exposure from medical treatment such as X-rays, particularly during puberty, increases risk, even at low doses.[17]

Medication. Hormone replacement therapy is a cause of breast cancer. The increased risk appears to disappear a few years after cessation.[18] Oral contraceptives containing both oestrogen and progesterone cause a small, transient, increased risk of breast cancer; the increased risk disappears after cessation.[19]

4. Interpretation of the evidence specific to breast cancer

4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7 of the Second Expert Report.

'Relative risk' is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.2 Specific

Considerations specific to breast cancer include:

Patterns. The preponderance of data from high-income countries is a special issue with breast cancer. Breast cancer is hormone related, and factors that modify risk have different effects on cancers diagnosed pre- and postmenopause.

Classification. Because of the importance of menopause as an effect modifier, studies should stratify for menopause status. Many do not.

Confounding. Hormone replacement therapy is an important possible confounder in postmenopausal breast cancer. A few studies also reported results separately for different hormone receptor profiles within cancers. High-quality studies adjust for age, number of reproductive cycles, age at which children were born, and the taking of hormone-based medications.

Effect modification. There is growing evidence that the impact of dietary exposures on risk of breast cancer may differ according to the particular molecular subtypes of cancer.

5. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report much of the methodology following for the Continuous Update Project remains unchanged from that used previously. Based upon the experience of conducting the systematic literature reviews for the Second Expert Report some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case-control studies. The 2008 Continuous Update Project Breast Cancer SLR included studies published up to December 2007. Publications in foreign languages were not included. Due to the large number of cohort studies, analysis and interpretation of case-control studies was not included in the Continuous Update Project SLR. Meta-analyses and forest plots of highest versus lowest categories were prepared for breast cancer incidence. Studies with mortality endpoints previously included in analyses were removed. Studies reporting mean difference as a measure of association are not included in the Continuous Update Project SLR as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies. (For more information on methodology see the full 2008 Continuous Update Project Breast Cancer SLR (Second Expert Report).

6. Evidence and judgements

The updated search identified 81 new articles, giving a total of 954 publications for breast cancer. The following sections include evidence from case-control studies considered as part of the Second Expert Report; however as mentioned in the previous section the evidence from case-control studies was not included in the 2008 Continuous Update Project Breast Cancer SLR. Fuller summaries of the experimental and mechanistic evidence can be found in chapters 4-6 of the Second Expert Report. For information on the criteria for grading the evidence see box 3.8 of the Second Expert Report. References to studies added in the Continuous Update Project have been included in the following sections; for details on references to other studies see Second Expert Report.

6.1 Alcoholic drinks

(Also see sections 3.7.1 Alcoholic drinks and 5.4 Alcohol (as ethanol) of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 4 new cohort studies[20-23] that investigated alcoholic drinks and 2 new cohort studies[24, 25] and 3 recent publications from previously included cohort studies[26-28] that investigated ethanol intake. For premenopausal breast cancer a total of 4 cohort studies investigated alcoholic drinks and 6 cohort studies investigated ethanol intake. The respective numbers for postmenopausal breast cancer were 9 and 16. For all-age breast cancer a total of 13 cohort studies investigated alcoholic drinks and 11 cohort studies investigated ethanol intake. Most studies showed increased risk with increased intake. Meta-analysis of cohort studies for the Second Expert Report showed a 10 per cent increased risk for all-age breast cancer, a 9 per cent increased risk for premenopausal breast cancer and a 8 per cent increased risk for postmenopausal breast cancer per 10 g ethanol (Page 167 Second Expert Report). An updated meta-analysis for postmenopausal breast cancer

showed an 8 per cent increased risk per 10 g ethanol (Figure A1 2008 Continuous Update Project Breast Cancer SLR). The Second Expert Report included 31 case-control studies that investigated alcoholic drinks and 29 case-control studies that investigated ethanol intake and all-age breast cancer. Meta-analysis of case-control data showed a 5 per cent increased risk per 5 drinks/week, and a 6 per cent increased risk per 10 g ethanol/day (Pages 166-167 Second Expert Report). Menopausal status did not significantly alter the association.

Two pooled analyses also showed statistically significant increased risks of 9 and 7 per cent per 10 g ethanol/day. The first was based on 6 cohort studies with more than 320 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases. The other analysed 53 case-control studies, with more than 58 000 cases and more than 95 000 controls.[29, 30] A meta-analysis of 3 cohort and 7 case-control studies assessed the association between alcohol intake and the risk of ER-/PR-defined breast cancer. [31] The dose-response meta-analysis showed that an increase in alcohol consumption of 10 g of ethanol per day was associated with statistically significant increased risks for all ER+ (12 per cent), all ER- (7 per cent), ER+PR+ (11 per cent) and ER+PR- (15 per cent), but not ER-PR-. A statistically significant heterogeneity of the results across all ER+ *versus* ER-PR- was observed.

Reactive metabolites of alcohol, such as acetaldehyde, may be carcinogenic. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. High consumers of alcohol may have diets deficient in essential nutrients, making tissues susceptible to carcinogenesis. In addition, most experimental studies in animals have shown that alcohol intake is associated with increased breast cancer risk. Alcohol interferes with oestrogen metabolism and action in multiple ways, influencing hormone levels and oestrogen receptors.

There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status partially mitigates the risk from increased alcohol consumption.[32]

The evidence added for the Continuous Update Project is consistent with that from the Second Expert Report. There is ample and generally consistent evidence from cohort and case-control studies.

A dose-response relationship is apparent. There is robust evidence for mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing. No threshold was identified.

6.2 Lactation

(Also see section 1.6.1 Breastfeeding of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 2 new cohort studies[33, 34] that investigated ever having breastfed as compared with never having breastfed and 3 new cohort studies[20, 21, 33] that investigated the total duration of lactation. For each of premenopausal and postmenopausal breast cancer a total of 2 cohort studies investigated ever having breastfed compared to never having breastfed and 2 cohort studies investigated total duration of lactation. For all-age breast cancer 3 studies investigated ever having breastfed and 6 studies investigated total duration of lactation. The Second Expert Report included 37 case-control studies that investigated ever having breastfed as compared with never having breastfed and 55 case-control studies that investigated the total duration of lactation. Most cohort and case-control studies reported decreased risk with ever having breastfed and with increasing duration of breastfeeding. Previous meta-analyses from the Second Expert Report for case-control data showed a 2 per cent decreased risk per 5 months of total breastfeeding; and for cohort data showed a non-significant decreased risk (Page 241 Second Expert Report). Pooled analysis from 47 epidemiological studies in 30 countries (more than 50 000 controls and nearly 97 000 breast cancer cases) showed a statistically significant decreased risk of breast cancer of 4.3 per cent for each 12 months of breastfeeding. Menopause status was not an effect modifier.[35] The relationship between breastfeeding and breast cancer according to hormone receptor status was investigated in a meta-analysis of 5 population-based case-control studies. A statistically significantly lower risk was found, both of ER+/PR+ breast cancers

(22 per cent) and for ER-/PR- cancers (26 per cent), for more than 6 months of breastfeeding compared with never breastfeeding. [36]

Lactation is associated with increased differentiation of breast cells and with lower exposure to endogenous sex hormones during amenorrhea accompanying lactation. In addition, the strong exfoliation of breast tissue during lactation, and the massive epithelial apoptosis at the end of lactation, could decrease risk by elimination of cells with potential DNA damage.

The evidence added for the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant epidemiological evidence from both cohort and case-control studies, which is consistent and shows a dose-response relationship. There is robust evidence for plausible mechanisms that operate in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that lactation protects against both premenopausal and postmenopausal breast cancer is convincing.

6.3 Physical activity

(Also see section 6. Physical Activity of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 2 new cohort studies[37, 38] investigating total physical activity; 1 new cohort study investigating occupational activity[37]; 3 new cohort studies[37-39] and 1 recent publication from a previously included cohort study[40] investigating recreational activity; and 2 new cohort studies[37, 38] investigating household activity. For premenopausal breast cancer a total of 5 cohort studies investigated total physical activity and 4, 3 and 1 studies investigated occupational, recreational and household activities respectively. For postmenopausal breast cancer 2 studies investigated total activity and 5, 11 and 1 studies investigated occupational, recreational and household activities respectively. For all-age breast cancer 4 studies investigated total physical activity and 4, 5 and 1 studies investigated occupational, recreational and household activities respectively. The Second Expert Report included 8 case-control studies that investigated total physical activity, 7 case-control studies that investigated occupational activity and 11 case-control studies that investigated recreational activity.

Menopause age unspecified

Most studies showed decreased risk with increased physical activity. Meta-analysis of case-control studies for the Second Expert Report showed a 10 per cent decreased risk per 7 MET-hours recreational activity/ week (Page 204 Second Expert Report).

Premenopause

Data were inconsistent for cohort studies for physical activity; however most case-control studies reviewed for the Second Expert Report showed evidence of decreased risk (Page 204 Second Expert Report).

Postmenopause

Nearly all of the cohort studies showed decreased risk with increased physical activity. The meta-analyses from the Second Expert Report of cohort and case-

control data both showed a 3 per cent decreased risk per 7 MET-hours recreational activity/week (Page 205 Second Expert Report).

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, it decreases levels of oestrogens and androgens in postmenopausal women. Some trials have also shown decreases in circulating oestrogens, increased menstrual cycle length, and decreased ovulation in premenopausal women with a high level of physical activity.

Premenopause: There is ample evidence from prospective studies, but it is inconsistent. There is evidence from case-control studies suggestive of a decreased risk with higher levels of physical activity. The conclusion reached for the Second Expert Report remains unchanged. There is limited evidence suggesting that physical activity protects against premenopausal breast cancer.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is ample evidence from prospective studies showing lower risk of postmenopausal breast cancer with higher levels of physical activity, with a dose-response relationship, although there is some heterogeneity. There is little evidence on frequency, duration, or intensity of activity. The conclusion reached for the Second Expert Report remains unchanged. There is robust evidence for mechanisms operating in humans. Physical activity probably protects against postmenopausal breast cancer.

6.4 Body fatness

(Also see section 8.1.1 Body Mass Index of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 10 new[34, 41-49] and 2 recent publications from previously included studies[39, 50] investigating body fatness, as measured by BMI for pre- and postmenopausal breast cancer. For premenopausal breast cancer there was a total of 22 studies and for postmenopausal breast cancer there were 28 studies. The Second Expert Report included more than 100 case-control studies that investigated body fatness. When grouped for all ages the Second Expert Report showed that the data were inconsistent in relationship to body fatness (Page 218 Second Expert Report) and this remained true for the Continuous Update Project. However, a consistent effect emerged when they were stratified according to menopausal status.

Premenopause

Most studies showed a decreased risk for premenopausal breast cancer. Meta-analyses for the Second Expert Report (Page 221 Second Expert Report) showed a 15 per cent decreased risk per 5kg/m^2 for cohort studies and an 8 per cent decreased risk per 5kg/m^2 for case-control studies; the updated meta-analysis for

cohort studies showed a 7 per cent decreased risk per 5kg/m^2 (Figure BMI4 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of four cohort studies with 723 cases of premenopausal breast cancer followed up for up to 11 years showed a 14 per cent decreased risk per 5kg/m^2.[51] A meta-analysis of 20 cohort studies reported an 8 per cent decreased risk per 5kg/m^2.[52]

Postmenopause

Most studies showed an increased risk for postmenopausal breast cancer with increased body fatness. Meta-analysis of cohort studies for the Second Expert Report (Page 219 Second Expert Report) showed an 8 per cent increased risk per 5kg/m^2 and a 13 per cent increased risk per 5kg/m^2; the updated meta-analysis of cohort studies showed a 13 per cent increased risk per 5kg/m^2 (Figure BMI7 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of seven cohort studies with 3208 cases of postmenopausal breast cancer followed up for up to 11 years showed a 9 per cent increased risk per 5kg/m^2.[51] A meta-analysis of 31 cohort studies reported a 12 per cent increased risk per 5kg/m^2.[52]

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (programmed cell death). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3 Second Expert Report). Adjusting for serum levels of oestradiol diminishes or destroys the association with BMI, suggesting that hormones are a predominant mechanism.[53]

There is no single well established mechanism though which body fatness could prevent premenopausal breast cancer. According to the oestrogen plus progesterone theory, overweight premenopausal women would be protected because they would be more frequently anovulatory, and therefore less likely to be exposed to endogenous progesterone. However, this theory is not well supported by recent studies, which suggest that natural progesterone could be protective.[54] Normal levels of natural progesterone are likely to be protective, and well nourished, or perhaps overnourished women, who may become slightly overweight in adulthood, may be protected by their natural fertile condition. Another possible mechanism is that the increased adipose tissue-derived oestrogen levels in overweight children could induce early breast differentiation and eliminate some targets for malignant transformation.[55] Anovulation and abnormal hormone profiles are commonly associated with obesity.[56] The age-specific pattern of association of breast cancer with BMI, therefore, is largely explained by its relationship with endogenous sex hormone levels.

Breast cancer diagnosed after the menopause is much more common. Therefore, throughout life, a decreased risk of premenopausal breast cancer would be outweighed by an increased risk of postmenopausal breast cancer.

Premenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is a substantial amount of consistent evidence epidemiological evidence with a dose-response relationship, but the mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. Greater body fatness probably protects against premenopausal breast cancer.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant and consistent epidemiological evidence and a clear dose-response relationship with robust evidence for mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that greater body fatness is a cause of postmenopausal breast cancer is convincing.

6.5 Adult attained height

(Also see section 8.3.1 Height of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 5 new cohort studies[34, 39, 41, 48, 57] that investigated adult attained height. The total number of cohort studies was 21 for all-age or age unspecified, 17 for premenopausal and 22 for postmenopausal breast cancer. The Second Expert Report included 29 case-control studies that investigated adult attained height and all-age breast cancer, 38 for premenopausal and 34 for postmenopausal breast cancer.

Menopausal age unspecified

Most of the studies showed increased risk. Meta-analysis for the Second Expert Report showed a 9 per cent increased risk per 5cm of height for cohort studies and a 3 per cent increased risk per 5cm of height for case-control studies (Page 233 Second Expert Report).

Premenopause

Most of the studies showed increased risk. Meta-analysis for the Second Expert Report showed a 9 per cent increased risk per 5cm of height for cohort studies and a 4 per cent increased risk per 5cm for case-control studies (Page 235 Second Expert Report). An updated meta-analysis of cohort studies also showed a 9 per increased risk per 5cm of height (Figure Ht1 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of four cohort studies with 723 cases of premenopausal breast cancer followed up for up to 11 years showed a non-significant increased risk with greater adult attained height.[51]

Postmenopause

Nearly all the cohort studies and most case-control studies showed increased risk, with no studies showing statistically significant contrary results. Meta-analyses for the Second Expert Report showed an 11 per cent increased risk per 5cm of height for cohort studies and a 2 per cent increased risk per 5cm for case-control studies (Page 234 Second Expert Report). An updated meta-analysis showed a 10 per increased risk per 5cm of height (Figure Ht4 2008 Continuous Update Project Breast Cancer SLR. A pooled analysis of seven cohort studies with

3208 cases of postmenopausal breast cancer followed up for up to 11 years showed a significantly significant 7 per cent increased risk per 5cm of height.[51]

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 and box 2.4 of the Second Expert Report. Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

Premenopause: There are fewer data for premenopausal than for postmenopausal breast cancer. The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. The epidemiological evidence is generally consistent, with a dose-response relationship and evidence for plausible mechanisms. The conclusion reached for the Second Expert Report remains unchanged. The factors that lead to greater adult height, or its consequences, are probably a cause of premenopausal breast cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant epidemiological evidence, which is generally consistent, with a clear dose-response relationship and evidence for plausible mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

6.6 Abdominal fatness (postmenopause)

(Also see sections 8.2.1 Waist Circumference and 8.2.3. and Waist to hip ratio of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 3 new cohort studies[42, 47, 48] and 1 recent publication from a previously included cohort study[58] that investigated waist circumference and 3 cohort studies[42, 47, 48] and 2 recent publications from previously included cohort studies[28, 59] that investigated waist to hip ratio. In total 9 cohort studies investigated waist circumference and 13 waist to hip ratio. The Second Expert Report included 3 case-control studies that investigated waist circumference and 8 that investigated waist to hip ratio.

All of the waist circumference studies and most of those on waist to hip ratio showed increased risk with increased measures of abdominal fatness. Meta-analysis of cohort studies for the Second Expert Report showed a 5 per cent increased risk per 8 cm in waist circumference (Page 226 Second Expert Report). The updated meta-analyses were stratified by whether the study adjusted for BMI. Studies that did not adjust for BMI showed a 7 per cent increased risk per 8cm in waist circumference and those that did showed a 4 per cent increased risk (Figures W5 and W6 2008 Continuous Update Project Breast Cancer SLR).

Meta-analysis of cohort studies for the Second Expert Report showed a 19 per cent increased risk per 0.1 increment in waist to hip ratio (Page 226 Second Expert Report). The updated meta-analyses were stratified by whether the study adjusted for BMI. Studies that did not adjust for BMI showed a 9 per cent increased risk per 0.1 increment in waist to hip ratio and those that did showed a non-significant increased risk (Figures WHR6 and WHR7 2008 Continuous Update Project Breast Cancer SLR).

The general mechanisms through which abdominal fatness could plausibly cause cancer are outlined in chapter 6.1.3 9 and box 2.4 of the Second Expert Report. The hormonal and other biological effects of being overweight or obese are outlined in chapter 8 of the Second Expert Report. Many of these, such as increased levels of circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is a substantial amount of epidemiological evidence but some inconsistency. There is robust evidence for mechanisms that operate in humans. The conclusion reached for the Second Expert Report remains unchanged. Abdominal fatness is a probable cause of postmenopausal breast cancer.

6.7 Adult weight gain (postmenopause)

(Also see section 8.1.6 Weight Change of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 3 new cohort studies[42, 47, 48] and 1 recent publication from a previously included cohort study[60] that investigated adult weight change and postmenopausal breast cancer. In total 10 cohort studies investigated adult weight change. The Second Expert Report included 17 case-control studies that investigated adult weight change. Nearly all the studies showed increased risk with increased weight gain in adulthood. Meta-analyses for the Second Expert Report showed a 3 per cent increased risk per 5kg gained for the cohort studies and a 5 per cent increased risk per 5kg for case-control studies (Page 227 Second Expert Report). Heterogeneity may be explained by failure to separate postmenopausal women taking hormone replacement therapy.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see chapter 2.7.1.3 Second Expert Report). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers.

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is ample, consistent epidemiological evidence and a dose-response relationship was apparent. The conclusion reached for the Second Expert Report remains unchanged. Adult weight gain is a probable cause of postmenopausal breast cancer.

6.8 Greater birth weight (premenopause)

(Also see section 8.4.1 Birthweight of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 1 new cohort study[61] that investigated birth weight and premenopausal breast cancer. In total 6 cohort and 4 case-control studies investigated birth weight. All cohort studies and most case-control studies showed increased risk with greater birth weight. Meta-analysis of cohort studies for the Second Expert Report showed an 8 per cent increased risk per kg (Page 238 Second Expert Report).

The general mechanisms through which the factors that lead to greater birth weight, or its consequences, could plausibly influence cancer risk are outline in chapter 6.2.11. of the Second Expert Report many of these, such as long-term programming of hormonal systems, could plausibly increase cancer risk. Greater birth weight raises circulating maternal oestrogen levels and may increase insulin-like growth factor (IGF)-1 activity; low birth weight raises fetal and maternal levels of IGF-1 binding protein. The action of both oestrogens and IGF-1 are thought to be important in fetal growth and mammary gland development, and play a central, synergistic role in the initiation and promotion of breast cancer.[62] Animal experiments also provide evidence that exposure to oestrogens during fetal and early postnatal development can increase the risk of mammary cancers.[63]

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is general consistency amongst the relatively few epidemiological studies, with some evidence for a dose-response relationship. The mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. The factors that lead to greater birth weight, or its consequences, are probably a cause of premenopausal breast cancer.

6.9 Total fat (postmenopause)

(Also see section 5.2 Total Fat of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 1 new cohort study[64] and 1 recent publication from a previously included cohort study[65] that investigated total fat intake and 1 new cohort study[66] and 1 recent publication from a previously included cohort study[67] that investigated energy from fat and postmenopausal breast cancer. In total 9 cohort studies investigated total fat intake and 5 cohort studies investigated energy from fat and postmenopausal breast cancer. The Second Expert Report included 16 case-control studies that investigated total fat intake and postmenopausal breast cancer. For total fat most studies showed increased risk with increased intake. Meta-analyses for the Second Expert Report showed a non-significant increased risk for cohort studies and an 11 per cent increased risk per 20g/day for case-control studies (Page 138 Second Expert Report). A pooled analysis of cohort studies of more than 7300 cases of breast cancer showed an overall non-significant decreased risk with increased fat intake. Menopausal status did not significantly alter the result.[68] For energy from fat

most cohort studies reported decreased risk with increasing per cent energy from fat and one reported a statistically significant increased risk.

The Women's Health Initiative Dietary Modification Randomised Controlled Trial with 655 cases of postmenopausal breast cancer reported a relative risk of 0.91 (0.83-1.01) for intervention and comparison group after 8.1 years.[69] Adjusting for change in body weight had no effect on the relative risk. The trial was designed to reduce fat intake to 20% and increase servings of vegetables and fruit to 5 per day and increase servings of grains to at least 6 per day. However for women with at least 36.8% energy from fat at baseline a decrease was observed for intervention compared with control (RR- 0.78 (0.64-0.95)).

Higher endogenous oestrogen levels after menopause are a known cause of breast cancer.[53, 70] Dietary fat may also increase endogenous oestrogen production.[71]

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. Evidence from prospective epidemiological studies of different types on the whole shows inconsistent effects, while case-control studies show a significant positive association. Mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. Overall, there is limited evidence suggesting that consumption of total fat is a cause of postmenopausal breast cancer.

6.10 Other exposures

For pre- and postmenopausal breast cancer, other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. The list of exposures is shown in the matrices under limited – no conclusion. Additional meta-analyses of cohort studies on dietary fibre and highest versus lowest category forest plots for total, red and processed meat, fish, dietary folate and energy were also conducted as part of the Continuous Update Project (See 2008 Continuous Update Project Breast Cancer SLR for details).

There is considerable speculation around a biologically plausible interaction of soy and soya products with breast cancer development, due to their high phytoestrogen content. Data on pulses (legumes) were sparse and inconsistent.

A meta-analysis of 3 cohort and 6 case-control studies showed a statistically significant 25 per cent lower risk of breast cancer at any age for highest versus lowest intake of soy products. [72]

A meta-analysis of 6 cohort and 12 case-control studies reported a statistically significant 14 per cent lower risk of breast cancer at any age for highest versus lowest consumption of soy protein (estimated from intake of soy food and dietary isoflavones). [73] Another meta-analysis reported a statistically significant 12 per cent lower risk of breast cancer at any age for highest versus lowest intake of isoflavones.[74] In a subgroup analysis the association was statistically significant for Asian populations (29 per cent lower risk) but not for Western populations. [74] These meta-analyses are limited by the difficulty in the standardisation of

measure of soy intake. The quantity and type of soy consumed varied greatly across the studies, such that the contrasts in intake levels for the reported risk estimates differed widely. Although results of these meta-analyses suggest that soy intake is associated with a modest reduction in breast cancer risk, heterogeneity across studies limits the ability to interpret the findings.

7. Comparison with the Second Expert Report

Overall the evidence from the additional cohort studies identified in the Continuous Update Project was consistent with those reviewed as part of the Second Expert Report. Much of the new evidence related to body fatness, abdominal fatness and weight gain; there were also new studies reporting on alcohol consumption.

8. Conclusions

Since the new evidence that was found as part of the Continuous Update Project is consistent with the evidence presented in the Second Expert Report the conclusions are unchanged.

The Continuous Update Project Panel concludes:

The evidence that lactation protects against breast cancer at all ages thereafter is convincing. Physical activity probably protects against postmenopausal breast cancer, and there is limited evidence suggesting that it protects against premenopausal breast cancer. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater attained adult height or its consequences are a cause of postmenopausal breast cancer is convincing; these are probably a cause of premenopausal breast cancer.

The factors that lead to greater birth weight or its consequences are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably a cause of this cancer. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

Acknowledgements

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Appendix 1 Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

This box lists the criteria finally agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

Convincing

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

Probable

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

All the following were generally required:

- Evidence from at least two independent cohort studies, or at least five case control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Evidence for biological plausibility.

Limited — suggestive

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The

evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.

All the following were generally required:

- Evidence from at least two independent cohort studies or at least five case control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

Limited — no conclusion

Evidence is so limited that no firm conclusion can be made. This category represents an entry level, and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited — no conclusion' for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (for example, lack of adjustment for known confounders), or by any combination of these factors.

When an exposure is graded 'limited — no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the Diet and Cancer Report website (www.dietandcancerreport.org). However, such evidence is usually not included in the summaries.

Substantial effect on risk unlikely

Evidence is strong enough to support a judgement that a particular food, nutrition, or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high versus low exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error,

including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias.
- Absence of a demonstrable biological gradient ('dose response').
- Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, an insufficient range of exposure in the study population, and inadequate statistical power. Defects in these and other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or in humans that a specific mechanism exists, or that typical exposures can lead to cancer outcomes, argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful, and could overlap with judgements of 'limited — suggestive' or 'limited — no conclusion'.

Special upgrading factors

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. So an exposure that might be deemed a 'limited — suggestive' causal factor in the absence, say, of a biological gradient, might be upgraded to 'probable' in its presence. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Continuous Update Project Breast Cancer 2010 Summary

World Cancer Research Fund International

www.wcrf.org

American Institute for Cancer Research

www.aicr.org

World Cancer Research Fund

www.wcrf-uk.org

Wereld Kanker Onderzoek Fonds

www.wcrf-nl.org

World Cancer Research Fund Hong Kong

www.wcrf-hk.org

www.dietandcancerreport.org

Continuous Update Project

CUP

Van: Germund Daal
Verzonden: vrijdag 21 augustus 2015 17:38
Aan: GR_RGV2015
Onderwerp: reactie Richtlijnen goede voeding 2015: Alcoholhoudende dranken

Geachte leden van de Commissie Richtlijnen goede voeding 2015,

Het Wereld Kanker Onderzoek Fonds (WKOF) maakt graag van de gelegenheid gebruik om een reactie te geven op het concept achtergronddocument 'Alcoholhoudende dranken' van de Gezondheidsraad.

Het Wereld Kanker Onderzoek Fonds maakt deel uit van het wereldwijde WCRF netwerk (World Cancer Research Fund). Het WCRF netwerk is een wereldwijd samenwerkingsverband van charitatieve organisaties die zich richten op de preventie van kanker door middel van een gezonde voeding en leefstijl. Het Wereld Kanker Onderzoek Fonds zet zich in Nederland sinds 1994 in voor kankerpreventie en heeft in 2007 samen met het WCRF netwerk een baanbrekend rapport gepubliceerd over het verband tussen voeding, leefstijl en kanker (Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Hierna aangeduid als het Second Expert Report). Dit is wereldwijd het meest uitgebreide rapport ooit over kankerpreventie.

Het Wereld Kanker Onderzoek Fonds/WCRF netwerk streeft ernaar continu over de meest recente inzichten over het verband tussen voeding, leefstijl en kanker te beschikken. Het Continuous Update Project (CUP) maakt dit mogelijk. Voor dit doorlopende onderzoeksproject worden alle bevindingen uit wereldwijd onderzoek naar de preventie en overleving van kanker door middel van voeding, gewicht en lichaamsbeweging geanalyseerd. Een onafhankelijk onderzoekspanel beoordeelt doorlopend de nieuwe bevindingen en trekt conclusies hierover. Jaarlijks verschijnen er nieuwe CUP rapporten op basis van meta-analyses waarbij prospectieve cohort studies de voorkeur hebben. Kortom, het CUP project van het WCRF netwerk biedt de meest actuele en grondige analyse van al het onderzoek naar voeding, leefstijl en kankerpreventie.

Vanuit onze specialisatie op het gebied van voeding, leefstijl en kankerpreventie reageert het Wereld Kanker Onderzoek Fonds graag op de conceptversie van de Gezondheidsraad over Alcoholhoudende dranken. In de bijlage vindt u onze reactie. De referenties van de wetenschappelijke rapporten en de achterliggende meta-analyses zijn tevens bijgevoegd, evenals hyperlinks voor het downloaden van de rapporten. De bestandsgrootte van de rapporten is namelijk te groot om ze allemaal per mail te sturen.

Het Wereld Kanker Onderzoek Fonds vertrouwt erop dat haar commentaar kan bijdragen aan de definitieve tekst voor de Richtlijnen goede voeding 2015. Indien u vragen heeft, laat ons dat dan graag weten.

Met vriendelijke groet,

Germund Daal
Hoofd Communicatie en Gezondheidsvoorlichting

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samen kanker voorkomen

Bijlage 1: Reactie Wereld Kanker Onderzoek Fonds

De reactie van het Wereld Kanker Onderzoek Fonds op het achtergronddocument van de Gezondheidsraad betreft het verband tussen alcohol en verschillende vormen van kanker (hoofdstuk 3.5 t/m 3.8). Het Wereld Kanker Onderzoek Fonds verwijst in haar commentaar naar het Second Expert Report en de CUP rapporten (bijlage 2, 4 en 9). Het CUP rapport Food, Nutrition, Physical Activity, and the Prevention of **Breast Cancer** is gebaseerd op een meta-analyse uit 2008. Het CUP rapport Food, Nutrition, Physical Activity, and the Prevention of **Colorectal Cancer** is gebaseerd op een meta-analyse uit 2010 (bijlage 5 en 10).

1. Onderscheid tussen typen drank: De Gezondheidsraad maakt in haar onderzoek naar alcohol en kanker onderscheid tussen bier, wijn en sterke drank (regel 406-735). Het WCRF netwerk evenals het International Agency for Research on Cancer (IARC) van de Wereldgezondheidsorganisatie maken echter geen onderscheid tussen verschillende soorten alcoholhoudende dranken omdat het verband tussen alcoholische dranken en kanker komt door ethanol, ongeacht welk type drank [1,2]. Het Wereld Kanker Onderzoek Fonds vraagt zich om deze reden af waarom de Gezondheidsraad ervoor heeft gekozen het onderzoek naar alcohol en kanker op te splitsen in verschillende soorten drank en adviseert om te kijken naar het verband tussen ethanol en kanker.

2. Darmkanker: De Gezondheidsraad ziet onvoldoende bewijskracht tussen alcohol uit sterke drank en het risico op darmkanker (regel 491-492). Het WCRF netwerk, evenals het IARC [2], ziet echter sterk wetenschappelijk bewijs voor een verband tussen alcohol en dikke darmkanker, ongeacht welk type alcoholische drank (RR 1.10 [1.06-1.13]) [3]. Het WCRF netwerk schat dat per jaar 7% van de nieuwe gevallen van dikke darm- en endeldarmkanker in westerse landen voorkomen kan worden door geen alcohol te drinken [4]. Dit zijn jaarlijks in Nederland naar schatting meer dan 1000 gevallen van darmkanker. Alcohol wordt sinds 1988 door het IARC erkend als "carcinogeen voor mensen" (indeling in Groep 1) [5]. In 2007 heeft het IARC darmkanker toegevoegd als kankersoort die causaal gerelateerd is aan alcoholgebruik [6]. Helaas ontbreken beide toonaangevende bronnen – het WCRF en het IARC – in de bronnenlijst van het document van de Gezondheidsraad. Het Wereld Kanker Onderzoek Fonds verzoekt de Gezondheidsraad dan ook om deze wetenschappelijke informatie toe te voegen aan het achtergrond document.

3. Borstkanker: De Gezondheidsraad vindt geen eenduidig bewijs voor het verband tussen alcoholische dranken en borstkanker (regel 520-521, 524-525, 528-529). Uit een analyse van het WCRF netwerk is echter reeds sterk wetenschappelijk bewijs naar voren gekomen over het verband tussen alcohol en borstkanker bij vrouwen, zowel premenopauzaal (RR 1.09 [1.01-1.17] [1] als postmenopauzaal (RR 1.08 [1.05-1.11]) [7]. Tevens heeft het IARC in 2007/2010 de conclusie getrokken dat alcohol een risicofactor is voor borstkanker [2]. Het WCRF netwerk schat dat per jaar 22% van de nieuwe gevallen van borstkanker in westerse landen voorkomen kan worden door geen alcohol te drinken [4]. Dit zijn jaarlijks in Nederland ongeveer 3200 gevallen. Het Wereld Kanker Onderzoek Fonds adviseert de Gezondheidsraad om deze wetenschappelijke informatie toe te voegen aan het achtergrond document en de conclusie over alcohol en borstkanker te herzien.

4. Andere kankersoorten gerelateerd aan alcohol: Andere kankersoorten die een relatie hebben met alcohol zijn niet opgenomen in de top 10 ziekten die de Gezondheidsraad onder de loep heeft genomen en staan dan ook niet in het achtergronddocument. Echter, uit analyses van het WCRF netwerk is gebleken dat alcohol een significante risicofactor is voor mond-, keel- en strottenhoofdkanker (RR

1.03 [1.02-1.04]) [1], slokdarmkanker (RR 1.04 [1.03-1.05]) [1] en leverkanker (RR 1.04 [1.02-1.06]) [8]. Tevens is in een toonaangevende publicatie van het IARC uit 1988 reeds geconcludeerd dat alcohol het risico op deze kankersoorten significant verhoogt [5]. Het Wereld Kanker Onderzoek Fonds raadt daarom de Gezondheidsraad aan deze kankersoorten wel te benoemen in het achtergrond document over alcoholhoudende dranken.

Concluderend
Zowel het IARC als het WCRF netwerk zijn op basis van analyses van het bestaande onderzoek tot de conclusie gekomen dat er 7 soorten kanker causaal gerelateerd zijn aan alcohol, te weten: dikke darmkanker, borstkanker, mondkanker, keelkanker, strottenhoofdkanker, slokdarmkanker en leverkanker. Het verband tussen alcohol en kanker is onafhankelijk van het type drank en betreft ethanol.

Het Wereld Kanker Onderzoek Fonds verzoekt de Gezondheidsraad deze informatie, gebaseerd op wereldwijd wetenschappelijk onderzoek, mee te nemen in de nieuwe Richtlijnen goede voeding 2015.

Referenties

1. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007. Ch 4.8 p 160-171. *Beschikbaar via: http://wkof.nl/sites/default/files/Second-Expert-Report.pdf*

2. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 96. Alcoholic beverage consumption and ethyl carbamate (urethane). Lyon: International Agency for Research on Cancer, 2010. *Beschikbaar via: http://monographs.iarc.fr/ENG/Monographs/vol96/index.php*

3a. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of **Colorectal Cancer**. 2011. p 20-22. *Beschikbaar via: http://wkof.nl/sites/default/files/Colorectal-Cancer-2011-Report.pdf*

3b. World Cancer Research Fund / American Institute for Cancer Research. **Colorectal Cancer** Systematic Literature Review. 2010. *Beschikbaar via http://www.wcrf.org/sites/default/files/SLR_colorectal_cancer_2010.pdf*

4. World Cancer Research Fund / American Institute for Cancer Research. Policy and Action for Cancer Prevention. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2009. *Beschikbaar via http://wkof.nl/sites/default/files/Policy_Report.pdf*

5. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the carcinogenic risks to humans. Volume 44. Alcohol Drinking. Lyon: International Agency for Research on Cancer, 1988. *Beschikbaar via http://monographs.iarc.fr/ENG/Monographs/vol44/mono44.pdf*

6. Baan et al. Carcinogenicity of alcoholic beverages. The Lancet Oncology. Volume 8, 2007. p 292-293. *Beschikbaar via http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045%2807%2970099-2.pdf*

7a. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of **Breast Cancer**. 2010. p 8-10. *Beschikbaar via http://wkof.nl/sites/default/files/Breast-Cancer-2010-Report.pdf*

7b. World Cancer Research Fund / American Institute for Cancer Research. **Breast Cancer** Systematic Literature Review. 2008. *Beschikbaar via http://www.wcrf.org/sites/default/files/SLR_breast_cancer.pdf*

8. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition, Physical Activity and **Liver Cancer**. 2015. p 22-27. *Beschikbaar via: http://wkof.nl/sites/default/files/Liver-Cancer-2015-Report.pdf*

Reactie van de commissie Richtlijnen goede voeding 2015 op het achtergronddocument over Alcoholhoudende dranken

De commissie heeft op het achtergronddocument over alcoholhoudende dranken reacties ontvangen van de Federatie Nederlandse Levensmiddelen Industrie (FNLI), het Kennisinstituut Bier, de Stichting Verantwoorde Alcoholconsumptie (STIVA), het Trimbos Instituut, het Nederlandse Instituut voor Alcoholbeleid (STAP), het Wereld Kanker Onderzoek Fonds (WKOF), dat deel uitmaakt van het World Cancer Research Fund (WCRF) en het Rijksinstituut voor Volksgezondheid en Milieu (RIVM). De commissie heeft de inhoudelijke reacties betrokken bij het opstellen van het definitieve achtergronddocument en over het algemeen de tekstuele suggesties overgenomen.

Twee conclusies zijn vervallen naar aanleiding van de ontvangen commentaren. Het betreft de conclusies over het verband tussen de consumptie van bier en wijn en het risico op hart- en vaatziekten.

Op de volgende pagina's beschrijft de commissie in een tabel alle inhoudelijke commentaren en wat zij daarmee heeft gedaan.

Tabel Overzicht ontvangen **inhoudelijke** commentaren op achtergronddocument over alcoholhoudende dranken en reactie van de commissie

Commentatoren	Commentaar	Reactie commissie
FNLI	Het is ons niet duidelijk geworden wat nu precies sterke drank is. Zijn dat alle dranken met een bepaald minimum percentage aan alcohol (en welk percentage geldt dan)? Is daarbij gecorrigeerd voor de aanwezigheid van andere voedingsstoffen (zoals bijvoorbeeld suikers in likeurdranken)? Zijn in alle studies de definities hetzelfde? Het is duidelijk bij de innamecijfers dat cider is meegeteld bij bier. Is de voedingswaarde echter gelijk afgezien van het alcoholgehalte? Is er rekening mee gehouden dat sommige bieren hogere gehaltes aan alcohol hebben dan andere? We vragen ons bovendien af in hoeverre het meetellen van versterkte wijnen zoals port en sherry bij 'wijn' de resultaten niet zullen vertekenen. Daarbij komt dan nog dat onduidelijk is of in de studies dezelfde dranken steeds zijn meegeteld als is weergegeven in de tabel met wat in Nederland wordt gedronken. Als laatste vragen we ons af in hoeverre bepaalde mixdrankjes zijn meegenomen in het achtergronddocument. Qua hoeveelheid alcohol per 100 gram bevinden deze zich dichter in de buurt van de wijnen dan de sterke drank hoewel ze vaak met sterke drank worden gemaakt.	Niet verwerkt In de aangehaalde publicaties wordt gerapporteerd over bier, wijn en sterke drank, maar zijn geen definities vermeld. Het klopt dat bij de innamegegevens in het achtergronddocument (tabel 1) de cijfers voor bier inclusief cider zijn en de cijfers over wijn inclusief versterkte wijnen; dit is in de voetnoten vermeld. Verschillen in alcoholgehaltes tussen verschillende soorten 'bier' en 'wijn' zijn wel verdisconteerd in de gegevens met betrekking tot alcohol uit drank, maar niet in de gegevens met betrekking tot de hoeveelheid drank. Mixdranken zijn in Tabel 1 buiten beschouwing gelaten. In het beschikbare cohortonderzoek zijn deze definities vaak niet duidelijk beschreven, omdat veel publicaties primair gericht waren op de totale alcoholinname. De analyses naar type alcoholhoudende drank zijn minder gedetailleerd toegelicht.
Kennisinstituut Bier	Allereerst wil ik aangeven dat het eerdere document: 'Concept Achtergronddocument Richtlijnen goede voeding 2015 - Alcohol' over het algemeen overeenkomt met onze interpretatie van de huidige wetenschappelijke stand van zaken. Het huidige achtergronddocument (Alcoholhoudende dranken) vertoont grote discrepanties met het achtergronddocument Alcohol. Dit is overigens niet verrassend omdat de epidemiologie niet in staat is drankspecifieke verschillen goed uit elkaar te trekken. Redenen hiervoor zijn de verschillen tussen een bier— en een wijndrinker die veelal niet worden meegewogen (een belangrijke factor is dieet) en het feit dat mensen nauwelijks alleen bier of alleen wijn drinken. We willen met onderstaand commentaar een constructieve bijdrage leveren aan	Niet verwerkt De keuze om zowel een achtergronddocument Alcohol als een achtergronddocument Alcoholhoudende dranken op te stellen, vloeit voort uit de werkwijze van de commissie.[2] De integratie van deze bevindingen gebeurt niet in de achtergronddocumenten, maar in het advies.

Commentatoren	Commentaar	Reactie commissie
	het document 'Concept Achtergronddocument Richtlijnen goede voeding 2015 - Alcoholhoudende dranken'. Echter, gezien de genoemde punten en daarmee de zwakheden in het onderzoek naar drankspecifieke effecten, adviseren wij dat u in overweging neemt om op basis van de huidige wetenschappelijke kennis geen onderscheid te maken in alcoholhoudende dranken en het voedingsadvies te richten op alcoholconsumptie in het algemeen zoals in de vorige editie van dé Richtlijnen goede voeding (2006) en zoals ook gedaan wordt in vele andere voedingsadviezen, zoals bijvoorbeeld die in de Dietary Guidelines for Americans, 2010.	
	Commentaar 1 (Interventieonderzoek):	
Kennisinstituut Bier	Ondanks uw bewuste keuze voor de intermediairen (bloeddruk, LDL cholesterol en BMI), willen wij aangeven dat het in het geval van alcoholconsumptie ook relevant is om te kijken naar HDL cholesterol verhoging[3],c.q. HDL gemedieerde cholesterol efflux[4] en ook zijn andere beschermende functies[5-8]. Daarnaast zijn er nog een aantal andere belangrijke factoren die een causaal verband aannemelijk maken, zoals fibrinogeen[3] en HbAlc[9] niet geëvalueerd. In al deze onderzoeken wordt geen onderscheid gevonden tussen alcoholhoudende dranken, waarmee dus gesuggereerd wordt dat het om een alcoholeffect gaat. lnterventieonderzoek maakt het zeer aannemelijk dat er een causaal verband is tussen matige alcoholconsumptie (dus geen drankspecifieke effecten) en een lagere incidentie van hart- en vaatziekten, zoals besproken in een systematisch review en meta-analyse[3] en cohort studies[10].	Niet verwerkt De aangedragen risicofactoren passen niet in de werkwijze van de commissie.[2]
Kennisinstituut Bier	Wat betreft effect op lichaamsgewicht is er in 2012 een meta-analyse verschenen van Bendsen en collega's over de relatie bierconsumptie en obesitas.[1]	Verwerkt De publicatie van Bendsen e.a.[1] is toegevoegd aan het achtergronddocument. Dit resulteert in een nieuwe paragraaf met een nieuwe conclusie: Er is te weinig onderzoek om een uitspraak te doen over het effect van bier op het lichaamsgewicht.

Commentatoren	Commentaar	Reactie commissie
	Commentaar 2 (Cohortonderzoek):	
Kennisinstituut Bier	Paragraaf 3.2.1: In het artikel van Ferrari wordt terecht gewezen op het volgende: *"In this study beer use displayed more apparent risk patterns than wine consumption, particularly in men. Although we believe that this finding is relevant, we call for cautious interpretations of these results, as the lifestyle profile of wine and beer drinkers is profoundly different."* Hiervoor verwijzen wij door naar commentaar 3 waarin ingegaan wordt op de eetpatronen van bier-, wijn- en gedistilleerd drinkers.	Niet verwerkt in paragraaf 3.2.1 In paragraaf 3.2 was al beschreven voor welke confounders in de beschikbare onderzoeken werd geadjusteerd. De tekst van deze paragraaf is niet aangepast. Een kanttekening over verschillen tussen bierdrinkers en wijndrinkers en het risico op restconfounding in de analyses specifiek voor type alcoholhoudende drank is toegevoegd aan paragraaf 3.1 'Methodologische kanttekeningen bij cohortonderzoek'.
Kennisinstituut Bier	Bij paragraaf 3.3.1 (Bier) wordt geconcludeerd dat een verband tussen bierconsumptie en het risico op hart- en vaatziekten onwaarschijnlijk is, terwijl in paragraaf 3.3.2 (Wijn) wel uitgebreid in wordt gegaan op de bevindingen uit het onderzoek van Costanzo[11] wat betreft wijn en hart- en vaatziekten. Costanzo en collega's schrijven in hun artikel: *"Unfortunately, the very limited data available about either beer or spirit consumption in relation to cardiovascular or total mortality, did not allow us to perform a fully meta-analytic investigation on the latter two beverages."* Met dit gegeven is het ons inziens onredelijk om het verband tussen bierconsumptie en het risico op hart- en vaatziekten als onwaarschijnlijk aan te duiden. Ook omdat de auteurs in de discussie specifiek aangeven: *"A previous meta-analysis had shown a clear inverse dose-effect curve against vascular events for wine but not for beer intake. Evidence from the current updated and extended meta-analysis confirms the significant reduction of overall vascular risk associated with wine consumption and shows, apparently for the first time, a similar J-shaped relationship between beer intake and cardiovascular risk. Moreover, the comparison of studies which included a parallel, separate evaluation of wine and beer consumption, indicates a similar protecting effect of either beverage against cardiovascular risk."*	Verwerkt Costanzo e.a.[11] includeerden in hun meta-analyse zowel cohortonderzoeken als patiëntcontrole onderzoeken. Ook de figuren die de vorm van het verband weergeven zijn op deze combinatie van cohortonderzoeken met patiëntcontrole-onderzoeken gebaseerd. Costanzo e.a. rapporteren een subgroepanalyses specifiek over de bevindingen van de cohortonderzoeken, maar daarin zijn bevindingen ten aanzien van verschillende uitkomstmaten samengevoegd (coronaire hartziekten, hart- en vaatziekten en totale sterfte). De bevindingen uit het onderzoek ten aanzien van totale sterfte[12] betreffen veruit het grootste aantal cases (7.208 sterfgevallen), daarom is deze subgroepanalyse niet bruikbaar voor de beschrijving van het verband met coronaire hartziekten (4.389 cases) of hart- en vaatziekten (1.145 cases). Een cohortonderzoek betreft volgens Costanzo e.a. myocard infarct, terwijl de publicatie over beroerte gaat.[13] Bovendien geven Costanzo e.a. aan dat zij de hoeveelheid drank presenteren, terwijl de gepresenteerde blootstellingen voor een deel van de publicaties betrekking heeft op de hoeveelheid alcohol in de drank. Vanwege genoemde kanttekeningen laat de commissie deze meta-analyse verder buiten beschouwing.
Kennisinstituut Bier	*Bij paragraaf 3.4 (Diabetes Mellitus type 2) wordt ons inziens onterecht geconcludeerd dat bierdrinkende mannen een hoger risico hebben op diabetes*	Niet verwerkt Het bespreken van plausibiliteit op basis van mechanistische overwegingen zoals

Commentatoren	Commentaar	Reactie commissie
	mellitus type 2 dan mannen die geen bier drinken en dat er geen verband is gevonden bij vrouwen, en dat er alleen met wijnconsumptie een geringe risicoverlaging is op diabetes mellitus type 2. Wij worden gesterkt in onze mening door de overall conclusie van dit onderzoek, waarbij vooral wordt ingegaan op een alcoholeffect en niet drankspecifieke effecten en de discussie waarin wordt aangegeven dat mogelijk leefstijl (zoals dieet) het verschil verklaart tussen de bier- en de wijndrinker (zie ook toelichting bij commentaar 3) [het Kennisinstituut Bier citeert de bevindingen van Beulens e.a.[14] ten aanzien van alcohol en vervolgt dan met de reflectie van deze auteurs over de verschillen tussen bier- en wijndrinkers:] "The specific risk reduction associated with wine consumption, however, appears to contradict the findings of several mechanistic studies. It was previously shown that the reduced risk of diabetes with moderate alcohol consumption can be explained by increased adiponectin concentrations for 25-30%. However, randomized trials in study populations consuming a variety of alcoholic beverages could not detect a difference in the effects on adiponectin concentrations. This suggests that the underlying biological mechanism is most probably explained by alcohol itself.	die met betrekking tot adinopectine valt buiten de werkwijze van de commissie.[2] De commissie baseert zich op verbanden met het ontstaan van chronische ziekten of met de sterfte en op effecten op bloeddruk, LDL-cholesterol en lichaamsgewicht.
	The specific risk reduction observed with wine could thus be attributed to other factors associated with wine consumption. Previous studies have shown that wine drinkers differ from drinkers of other beverages by consuming a healthier diet and being less likely to smoke. As men and women may also differ with regard to such health-related behaviours, as is seen in the different structure of confounders amongst men and women, this could in part explain the specific association observed for wine consumption and the different effects between men and women."	Niet verwerkt in paragraaf 3.4 In paragraaf 3.4 was al beschreven voor welke confounders in de beschikbare onderzoeken werd geadjusteerd. De tekst van deze paragraaf is niet aangepast. Een kanttekening over verschillen tussen bierdrinkers en wijndrinkers en het risico op restconfounding in de analyses specifiek voor type alcoholhoudende drank is toegevoegd aan paragraaf 3.1 'Methodologische kanttekeningen bij cohortonderzoek'.
Kennisinstituut Bier	Paragraaf 3.6 Borstkanker: Het feit dat er in het achtergronddocument 'Alcohol' wel een grote bewijskracht wordt gevonden aangaande alcoholconsumptie en risico op borstkanker bij vrouwen, terwijl in het achtergronddocument	Niet verwerkt De commissie beschrijft in een ander achtergronddocument de bevindingen ten aanzien van alcohol. De integratie van conclusies uit de achtergronddocumenten in

<table>
<tr><th>Commentatoren</th><th>Commentaar</th><th>Reactie commissie</th></tr>
<tr><td></td><td>Alcoholhoudende dranken voor geen van de alcoholhoudende dranken een eenduidige uitkomst wordt gevonden, is tegenstrijdig. Smith-Warner en collega's geven aan: "The specific type of alcoholic beverage did not strongly influence risk estimates." Tjønneland en collega's concluderen: "This large European study supports previous findings that recent average alcohol intake, irrespectively of beverage type, increases the risk of breast cancer." Deze bevindingen sterken nogmaals onze overtuiging dat het gaat om een alcoholeffect en dat daarom een voedingsadvies op basis van alcoholconsumptie en niet gespecificeerd per drank de voorkeur heeft.</td><td>niet aan de orde in de achtergronddocumenten, maar in het advies.</td></tr>
<tr><td></td><td>Commentaar 3 (Bier-, wijn- en gedistilleerddrinkers en hun verschillen)</td><td></td></tr>
<tr><td>Kennisinstituut Bier</td><td>Een belangrijke reden om geen onderscheid te maken tussen een bier-, wijn- en gedistilleerddrinker, is omdat deze nagenoeg niet bestaan. Er wordt nauwelijks alleen bier of alleen wijn of alleen gedistilleerd gedronken. Dit blijkt ook uit onderzoek van Sluik en collega's.[15] Zij hebben deelnemers aan de VCP 2007-2010 ingedeeld naar drankvoorkeur, waarbij als criterium is gebruikt dat als 70% van de consumptie bestond uit wijn, dan wel bier, dan wel gedistilleerd, men respectievelijk een wijn-, bier-, gedistilleerd drinker is. Als het aantal glazen bier, wijn of gedistilleerd niet optelde tot 70%, dan had men geen voorkeur. Op basis van deze, overigens niet officieel bestaande, definitie waren de drankvoorkeuren als volgt:
<table>
<tr><th></th><th colspan="3">Voorkeur voor</th><th>Geen voorkeur</th><th>Geen alcohol</th></tr>
<tr><th></th><th>Bier</th><th>Wijn</th><th>Gedistilleerd</th><th></th><th></th></tr>
<tr><td>Man</td><td>32%</td><td>10%</td><td>5%</td><td>33%</td><td>20%</td></tr>
<tr><td>Vrouw</td><td>5%</td><td>26%</td><td>6%</td><td>22%</td><td>41%</td></tr>
</table>
Verder hebben Sluik en collega's in hetzelfde onderzoek gekeken naar de eetpatronen van de op deze manier gedefinieerde bier-, wijn- en gedistilleerd drinkers.'[16] Mensen met een voorkeur voor bier hadden ongezondere eetgewoonten dan mensen met een voorkeur voor wijn. Hierdoor is het dus niet</td><td>Niet verwerkt
In de analyses betreffende de verbanden met de consumptie van bier, wijn of sterke drank met het risico op chronische ziekten wordt doorgaans geadjusteerd voor het gebruik van andere typen alcoholhoudende drank.

Verwerkt
In paragraaf 3.1 'Methodologische kanttekeningen bij cohortonderzoek' is een alinea toegevoegd over verschillen tussen bierdrinkers en wijndrinkers en het risico op restconfounding in de analyses specifiek voor type alcoholhoudende drank.</td></tr>
</table>

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	uitgesloten dat dieet een confounder is in de relatie tussen alcoholconsumptie en gezondheid, waarvoor veelal niet wordt gecorrigeerd. Dat zou een reden kunnen zijn dat de zogenoemde bierdrinkers er daarom 'slechter' vanaf komen dan de zogenoemde wijndrinkers. Ook uit een systematische review door Sluik en collega's blijkt dat drankvoorkeur gerelateerd is aan eetgewoonten. Zij concluderen dat als er specifiek naar drankvoorkeur gekeken wordt in relatie tot gezondheid, voeding zeker moet worden meegenomen als confounder aangezien onderliggende voedingsvoorkeuren vaak eerder gerelateerd zijn aan gezondheid dan het type drank.	Niet verwerkt De systematische review van Sluik en collega's kan niet worden aangehaald in het achtergronddocument, omdat deze nog niet is verschenen.
STIVA	Er bestaat een groot aantal discrepanties tussen de conclusies getrokken in de achtergronddocumenten 'alcohol' en 'alcoholhoudende dranken'. Daarom menen wij dat conclusies met betrekking tot dranktypen niet kunnen bijdragen aan een eventueel advies over de consumptie van specifieke dranktypen. Onduidelijk is dus hoe de verschillen tussen de uitkomsten gerapporteerd in het achtergronddocument alcoholhoudende dranken en de uitkomsten gerapporteerd in het achtergronddocument alcohol moeten worden geïnterpreteerd. Men zou immers een grote overeenkomst verwachten tussen de uitkomsten van de beide documenten. Dit is echter niet het geval; er zijn tegenstrijdigheden en veel informatie ontbreekt. De volgende tegenstrijdigheden vallen op in de conclusies van de beide documenten (zie ook Tabel 1). [STIVA beschrijft hierna puntsgewijs 9 strijdigheden en voegt een overzichtstabel van conclusies met grote bewijskracht in de achtergronddocumenten 'alcohol' en 'alcoholhoudende dranken' bij.]	Niet verwerkt De integratie van bevindingen tot een richtlijn ten aanzien van het alcoholgebruik is niet aan de orde in het achtergronddocument. Deze gebeurt in het advies.
STIVA	Een belangrijke methodologische kanttekening die wordt gemist is de correctie voor verstoring (confounding) in de vergelijking tussen de effecten van bier, wijn en gedistilleerde dranken. Een van de grote problemen bij het bestuderen van de effecten van de afzonderlijk alcoholhoudende dranken is dat de meeste	Niet verwerkt In de analyses betreffende de verbanden met de consumptie van bier, wijn of sterke drank met het risico op chronische ziekten wordt doorgaans geadjusteerd voor het gebruik van andere typen alcoholhoudende drank en daarnaast voor potentiële

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	consumenten zowel bier als wijn als gedistilleerd drinken; het komt zelden voor dat één dranktype uitsluitend wordt geconsumeerd. Veelal (ook in de studies vermeld in dit achtergronddocument) wordt een rekenkundige bewerking uitgevoerd om toch een effect van één specifieke dranksoort te kunnen afleiden. Een dergelijke bewerking houdt geen rekening met variaties in drinkpatronen (dagelijks wijn of wekelijks bier / voor of bij de maaltijd drinken) en variaties in andere factoren (geslacht; vrouwen drinken meestal wijn / leeftijd) en heeft dus tekortkomingen. Een directe vergelijking van de effecten van de drie dranktypen op de gezondheid uitsluitend door middel van epidemiologisch onderzoek heeft dus grote methodologische nadelen en is dus niet verantwoord te maken.	confounders zoals geslacht, BMI, opleidingsniveau en rookgedrag. De rekenkundige bewerking houdt dus tevens rekening met variaties in deze potentiële confounders. In het achtergronddocument is voor de gepoolde analyses steeds beschreven voor welke potentiële confounders in de onderzoeken was geadjusteerd. Voor de meta-analyses is dat niet mogelijk, omdat daarbij wordt uitgegaan van de analyseresultaten uit de oorspronkelijke publicaties, waarbij de mate van adjustering tussen de publicaties verschilt. STIVA merkt terecht op dat in de publicaties die in dit achtergronddocument zijn aangehaald, doorgaans niet is geadjusteerd voor drinkpatronen (binge drinken, alcoholgebruik tijdens de maaltijd of juist buiten de maaltijden), maar dat is evenmin het geval in de meeste publicaties over verbanden tussen het totale alcoholgebruik en het risico op chronische ziekten. Deze kanttekening is dus van toepassing op beide achtergronddocumenten (Alcohol en Alcoholhoudende dranken).
STIVA	Een tweede belangrijke methodologische kanttekening betreft de correctie van de overige leefstijlfactoren (met name dieet) bij typische bierconsumenten, wijnconsumenten en consumenten van sterke drank. Een beroemd voorbeeld is de studie door Grønbaek[17], die een duidelijk gezondheidsvoordeel liet zien voor de wijndrinker in vergelijking met de bierdrinker en de gedistilleerddrinker. Deze studie is later opnieuw geanalyseerd met een uitgebreidere correctie voor de voeding van de diverse typen drinkers[18]; door deze correctie verdwenen de verschillen tussen bier, wijn en gedistilleerd helemaal. De rol van confounding in de relatie tussen dranktype en gezondheidsuitkomst is daarna nog eens door deze groep bevestigd.[19] Het is dus zeer waarschijnlijk dat de wijndrinker een andere leefstijl(met name voeding) heeft dan de bierdrinker, waardoor de uitkomsten worden verstoord. Overigens noemen Ferrari e.a.[20] dit probleem ook in hun discussie: ‘Although we believe that this finding is relevant, we call for cautious interpretations of these results, as the lifestyle profile of wine and beer drinkers is profoundly different.’	Verwerkt In paragraaf 3.1 ‘Methodologische kanttekeningen bij cohortonderzoek’ is een alinea toegevoegd over verschillen tussen bierdrinkers en wijndrinkers en het risico op restconfounding in de analyses specifiek voor type alcoholhoudende drank.

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STIVA	Andere grote onderzoeken en reviews die geen effect van dranktype laten zien (op totale sterfte en coronaire hartziekten (paragrafen 3.2 en 3.3) worden niet mede overwogen in dit achtergronddocument. Deze onderzoeken zijn toegevoegd aan de referentielijst van dit commentaar.[21-25]	
	• Mukamal e.a.[21] concluderen: *"Among men, consumption of alcohol at least three to four days per week was inversely associated with the risk of myocardial infarction. Neither the type of beverage nor the proportion consumed with meals substantially altered this association. Men who increased their alcohol consumption by a moderate amount during follow-up had a decreased risk of myocardial infarction."*	Niet verwerkt Deze publicatie is geïncludeerd in de meta-analyse van Costanzo e.a. en wordt dus niet als aanvullend cohortonderzoek toegevoegd.
	• Rimm e.a.[22] concluderen in hun meta-analyse: *"Although most ecological studies support the hypothesis that wine consumption is most beneficial, the methodological problems of these studies limit their usefulness in drawing conclusions. Most of the differences in findings regarding specific drink types are probably due to differences in patterns of drinking specific types of alcoholic drink and to differing associations with other risk factors. Results from observational studies, where individual consumption can be assessed in detail and linked directly to coronary heart disease, provide strong evidence that a substantial proportion of the benefits of wine, beer, or spirits are attributable primarily to the alcohol content rather than to other components of each drink."*	Niet verwerkt De meta-analyse van Rimm e.a. uit 1996[22] is gedateerd en wordt aangehaald in de publicatie van Costanzo e.a.[11]
	• Cleophas[23] concludeert uit zijn systematische review: *"1. Small doses of alcohol (1-4 drinks a day) are associated with a slightly reduced risk of mortality and coronary heart disease (CHD). 2. Small doses (1-4 drinks a day) of wine, beer, and spirits are equally beneficial. 3. Apart from a direct beneficial effect of low doses of alcohol on mortality and CHD, some psychological factors may contribute to its beneficial effect."*	Niet verwerkt De systematische review van Cleophas uit 1999[23] is eveneens gedateerd; deze wordt niet aangehaald in de publicatie van Costanzo e.a.[11]
	• Tolstrup en Gronbaek concluderen in hun review[24]: *"Finally, there is some*	Niet verwerkt

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	evidence that wine may have more beneficial effects than beer and distilled spirits; however, these results are still controversial and may be confounded by personal characteristics and other lifestyle factors such as diet. The inverse association between alcohol intake and CHD is influenced by age, gender, drinking pattern, and possibly by type of alcohol." • Klatsky e.a.[25] concluderen: *"We conclude that (1) drinking ethyl alcohol apparently protects against coronary disease, and (2) there may be minor additional benefits associated with drinking both beer and wine, but not especially red wine...etc."*	De publicatie van Tolstrup en Gronbaek[24] is geen systematische review. Niet verwerkt Deze publicatie verscheen ruim voor de meta-analyse van Costanzo e.a.[11] en wordt niet als aanvullend cohortonderzoek toegevoegd.
STIVA	De conclusies in het achtergronddocument 'alcoholhoudende dranken' in de paragrafen 3.2 en 3.3 zijn gebaseerd op een enkele meta-analyse[11] die een uitgebreidere versie is van een eerdere meta-analyse door grotendeels dezelfde groep epidemiologen[26]. Door de uitbreiding van de meta-analyse komen de auteurs tot een herziene conclusie. Costanzo e.a.[11] concluderen (zie abstract): *"In previous studies evaluating whether different alcoholic beverages would protect against cardiovascular disease, a J-shaped relationship for increasing wine consumption and vascular risk was found; however a similar association for beer or spirits could not be established. An updated meta-analysis on the relationship between wine, beer or spirit consumption and vascular events was performed. … … From 16 studies, evidence confirms a J-shaped relationship between wine intake and vascular risk. … … Similarly, from 13 studies a J-shaped relationship was apparent for beer.(..). From 12 studies reporting separate data on wine or beer consumption, two closely overlapping dose-response curves were obtained (maximal protection of 33% at 25 g/day of alcohol). This meta-analysis confirms the J-shaped association between wine consumption and vascular risk and provides, for the first time, evidence for a similar relationship between beer and vascular risk. In the meta analysis of 10 studies on spirit consumption and vascular risk, no J-shaped relationship could be found."*	Verwerkt Costanzo e.a.[11] includeerden in hun meta-analyse zowel cohortonderzoeken als patiëntcontrole onderzoeken. Ook de figuren die de vorm van het verband weergeven zijn op deze combinatie van cohortonderzoeken met patiëntcontrole-onderzoeken gebaseerd. Costanzo e.a. rapporteren een subgroepanalyse specifiek over de bevindingen van de cohortonderzoeken, maar daarin zijn bevindingen ten aanzien van verschillende uitkomstmaten samengevoegd (coronaire hartziekten, hart- en vaatziekten en totale sterfte). De bevindingen uit het onderzoek ten aanzien van totale sterfte[12] betreffen veruit het grootste aantal cases (7.208 sterfgevallen), daarom is deze subgroepanalyse niet bruikbaar voor de beschrijving van het verband met coronaire hartziekten (4.389 cases) of hart- en vaatziekten (1.145 cases). Een cohortonderzoek betreft volgens Costanzo e.a. myocard infarct, terwijl de publicatie over beroerte gaat.[13] Bovendien geven Costanzo e.a. aan dat zij de hoeveelheid drank presenteren, terwijl de gepresenteerde blootstellingen voor een deel van de publicaties betrekking heeft op de hoeveelheid alcohol in de drank. Vanwege genoemde kanttekeningen laat de commissie deze meta-analyse verder buiten beschouwing.

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	De auteurs melden in de discussie bovendien dat data voor bier- en gedistilleerd-consumptie nog steeds beperkt zijn: *"Unfortunately, the very limited data available about either beer or spirit consumption in relation to cardiovascular or total mortality, did not allow us to perform a fully meta-analytic investigation on the latter two beverages."* De conclusie geformuleerd door de auteurs is dus anders dan de conclusie weergegeven in het achtergronddocument (paragraaf 3.3.1). Deze laatste is gebaseerd op een andere analyse, een deelanalyse, uit hetzelfde artikel. Het is vooralsnog onduidelijk waarom het achtergronddocument deze analyse volgt en op basis van deze analyse de relatie tussen bierconsumptie en hart- en vaatziekten risico aanduidt als een onwaarschijnlijk verband en niet de uiteindelijke conclusie van de auteurs volgt.	
STIVA	Een derde belangrijke methodologische kanttekening wordt terecht gemaakt op pagina 7, namelijk dat er kritische opmerkingen zijn gemaakt over de controle groepen (geheelonthouder) in cohortonderzoeken (Fillmore e.a.[27]) naar de associatie tussen alcohol en ziekte uitkomsten. Het is echter voor de volledigheid goed te vermelden dat cohorten die wel een onderscheid hebben kunnen maken tussen niet-drinkers en ex-drinkers in hun controle groep, geen essentiële verschillen vonden in de beschreven associaties.[28-31] Het 'sick quitters' argument lijkt dus niet te gelden. Ook wanneer de controle niet uit geheelonthouders bestaat maar uit lichte drinkers zijn er verdere dalingen van het risico beschreven.[32,33]	Niet verwerkt De bevindingen uit de referenties met betrekking tot het sick quitters argument[28-33], hebben betrekking op het totale alcoholgebruik en niet op het gebruik van bier, wijn of sterke drank. Daarom passen ze niet in dit achtergronddocument.
STIVA	Met betrekking tot het interventieonderzoek, begrijpen we de keuze voor de intermediairen (bloeddruk, LDL cholesterol en BMI) zoals die wordt omschreven in het document 'werkwijze van de commissie richtlijnen goede voeding 2015'. Wij betreuren de gekozen benadering echter in het geval van dit specifieke achtergronddocument. HDL cholesterol verhoging, c.q. HDL gemedieerde cholesterol efflux[4] en andere HDL functies worden niet meegewogen in het hoofdstuk 2: Interventieonderzoek.	Niet verwerkt De aangedragen risicofactoren (HDL-cholesterol, HDL gemedieerde cholesterol efflux[3-8], fibrinogeen en HbAlc[34]) passen niet in de werkwijze van de commissie.[2]

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	Deze keuze is gemaakt omdat medicijnen en niacine die HDL cholesterol verhogen, niet aantoonbaar bijdragen aan het voorkomen van hartaanvallen. Er zijn echter een beperkt aantal geneesmiddelen getest dat HDL cholesterol verhoogt, c.q. HDL functie verbetert en alcohol (net als lichamelijke activiteit) is een van de weinige nutriënten die niet alleen HDL cholesterol verhoogt maar ook zijn beschermende functies positief beïnvloedt.[5-8] HDL wordt in dezelfde mate verhoogd door bier, wijn en gedistilleerd[3,7],evenals de meeste andere intermediairen zoals gerapporteerd in de meta-analyse van Brien[3]. Bovendien wordt door het volgen van de cases geëvalueerd door het IOM[34] een aantal andere belangrijke factoren die een causaal verband aannemelijk maken, zoals fibrinogeen en HbAlc niet geëvalueerd. Door deze benadering kan de commissie geen conclusie trekken over de effecten van alcoholhoudende dranken op geen enkele intermediair (zelfs niet LDL cholesterol, noch bloeddruk). Interventie onderzoek maakt echter zeer aannemelijk dat er een causaal verband is tussen consumptie van matige hoeveelheden alcoholhoudende dranken en een lagere incidentie van hart- en vaatziekten, zoals besproken in een systematisch review en meta-analyse[3] en cohort studies[10].	
STIVA	In het werkwijze document wordt gesteld dat de commissie zich in beginsel beperkt in haar literatuuronderzoek tot een kritische evaluatie van gepoolde analyses, meta-analyses en systematische reviews die gepubliceerd zijn in peer-reviewed tijdschriften. In gepoolde analyses en meta-analyses worden de bevindingen uit meerdere oorspronkelijke onderzoeken met overeenkomstige vraagstelling en aanpak gecombineerd tot een nieuwe risicoschatting. Echter de conclusies met betrekking tot totale sterfte zijn gebaseerd op één multicenter studie[20], die wellicht voldoet aan het criterium 'gepoolde analyse', maar niet aan het criterium 'bevindingen uit meerdere oorspronkelijke onderzoeken gecombineerd tot een nieuwe risicoschatting'. Toch wordt de	Niet verwerkt De multicenter studies van de European Prospective Investigation into Cancer and Nutrition van Ferrari e.a.[20] voldoen aan het criterium van een gepoolde analyse. De commissie beschouwt de cohorten binnen EPIC als onafhankelijke cohortonderzoeken. In gepoolde analyses worden de risicoschatters van alle cohorten op identieke wijze geadjusteerd voor potentiële confounders en daarna samengevoegd. In meta-analyses worden risicoschatters samengevoegd zoals die in de geïncludeerde publicaties zijn gerapporteerd. Nadeel van een meta-analyse ten opzichte van een gepoolde analyse is, dat de mate van adjustering voor confounders in een meta-analyse verschilt tussen de geïncludeerde

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	bewijskracht als 'groot' omschreven.	risicoschattingen; voordeel van een meta-analyse ten opzichte van een gepoolde analyse is, dat het in principe mogelijk is om al het relevante beschikbare onderzoek te includeren. Zowel meta-analyses als gepoolde analyses kunnen – afhankelijk van het beschikbare onderzoek en de bevindingen - aanleiding geven tot conclusies met grote bewijskracht.
STIVA	Het is opvallend dat met betrekking tot Diabetes Mellitus type 2 (paragraaf 3.4), op basis van het onderzoek van Beulens e.a.[14] het achtergronddocument conclusies trekt over de verschillende dranktypen, terwijl de auteurs conclusies trekken over 'moderate alcohol consumption' en niet over drank specifieke effecten. De auteurs merken in hun discussie op: *"The specific risk reduction associated with wine consumption, however, appears to contradict the findings of several mechanistic studies. It was previously shown that the reduced risk of diabetes with moderate alcohol consumption can be explained by increased adiponectin concentrations for 25-30%[35]. However, randomized trials in study populations consuming a variety of alcoholic beverages could not detect a difference in the effects on adiponectin concentrations.[36-39] This suggests that the underlying biological mechanism is most probably explained by alcohol itself.* *The specific risk reduction observed with wine could thus be attributed to other factors associated with wine consumption. Previous studies have shown that wine drinkers differ from drinkers of other beverages by consuming a healthier diet and being less likely to smoke.[40] As men and women may also differ with regard to such health-related behaviours, as is seen in the different structure of confounders amongst men and women, this could in part explain the specific association observed for wine consumption and the different effects between men and women."*	Niet verwerkt De opmerking met betrekking tot adinopectine[35-39] betreft een hypothese betreffende een werkingsmechanisme. Het past niet in de werkwijze van de commissie om hier op in te gaan.[2] De conclusies van de commissie op basis van de gepoolde analyse van Beulens e.a. (European Prospective Investigation into Cancer and Nutrition)[14] betreffen een substantieel aantal cohorten en cases en zijn geformuleerd conform de werkwijze van de commissie.[2] Verwerkt In paragraaf 3.1 'Methodologische kanttekeningen bij cohortonderzoek' is een alinea toegevoegd over verschillen tussen bierdrinkers en wijndrinkers en het risico op restconfounding in de analyses specifiek voor type alcoholhoudende drank.
STIVA	In paragraaf 3.4 wordt herhaaldelijk gerefereerd aan 'aanvullend onderzoek' van Cullmann[41] en telkens wordt vermeld dat het onderzoek een te beperkt aantal cases betreft om daar conclusies op te baseren. Wellicht kan dit onderzoek	Niet verwerkt De beschrijving is conform de werkwijze van de commissie.[2]

Commentatoren	Commentaar	Reactie commissie
	worden verwijderd of minder worden benadrukt.	
Trimbos Instituut	De vraag of gedistilleerd, bier of wijn van invloed is op de morbiditeit in het algemeen en kanker in het bijzonder lijkt ons moeilijk te beantwoorden op basis van epidemiologisch onderzoek. Een standaardglas gedistilleerd, bier of wijn bevat allemaal een zelfde hoeveelheid pure alcohol (10 gram in Nederland) en hoewel verschillend qua concentratie alcohol in de drank, leiden ze tot een zelfde BAC in het lichaam. De stof alcohol en het afbraakproduct van alcohol acetaldehyde worden beiden als carcinogeen aangemerkt. Hoewel consumenten voorkeur kunnen hebben voor een specifieke alcoholhoudende drank (wijn, bier of gedistilleerd), worden in de praktijk diverse alcoholhoudende dranken door elkaar heen gedronken (bijvoorbeeld wijn in combinatie met een aperitief en cognac).	Niet verwerkt In dit achtergronddocument beschrijft de commissie de specifieke bevindingen ten aanzien van bier, wijn en sterke drank. In het achtergronddocument Alcohol zijn de bevindingen ten aanzien van het totale alcoholgebruik beschreven. De integratie van bevindingen en het opstellen van een richtlijn is aan de orde in het advies.
Trimbos Instituut	We zijn verbaasd dat de relatie tussen alcohol en borstkanker als niet eenduidig wordt gekenmerkt. We zijn benieuwd wat u precies bedoelt met niet eenduidig. Volgens onze lezing van de literatuur is de relatie tussen borstkanker en alcoholconsumptie wel eenduidig en dit is onder andere gebaseerd op bijgevoegde literatuur.[42-45]	Niet verwerkt Het achtergronddocument ‘Alcoholhoudende dranken’ gaat niet over het verbanden met het totale alcoholgebruik, maar over verbanden met het gebruik van bier, wijn of sterke drank. Voor deze specifieke typen alcoholhoudende drank heeft de commissie geen eenduidige verbanden met het risico op borstkanker gevonden. De commissie is het met u eens dat het verband van een hoger alcoholgebruik met een hoger risico op borstkanker grote bewijskracht heeft; dit is beschreven in het achtergronddocument ‘Alcohol’. De integratie van bevindingen en het opstellen van een richtlijn is niet aan de orde in de achtergronddocumenten, maar in het advies. De door Trimbos bijgevoegde referenties zijn niet toegevoegd om de volgende redenen: • Cao e.a.[42] verscheen in juli 2015 en betreft analyses van resultaten van de twee afzonderlijke cohorten. Het is geen gepoolde analyse of meta-analyse. Deze publicatie valt buiten de periode van het literatuuronderzoek voor het achtergronddocument en wordt daarom niet meegenomen. • De publicatie van Hamajima e.a. (van de Collaborative Group on Hormonal
STAP	Wij hebben ernstige twijfels bij de conclusie in het rapport dat er geen eenduidig verband zou bestaan tussen alcoholgebruik en het ontstaan van borstkanker bij vrouwen. In de bijlage bij deze reactie sturen we twee recente artikelen mee waarin duidelijke uitspraken worden gedaan over de samenhang tussen alcoholgebruik en het ontstaan van borstkanker en waarbij geen sprake is van het ontbreken van een eenduidig verband.	
	Wat ons verontrust is dat in uw rapport steeds nadrukkelijk onderscheid wordt gemaakt tussen wat bekend is over de relatie tussen borstkanker (en ook in geval van andere ziekten) en wijngebruik, borstkanker en biergebruik en borstkanker en het gebruik van sterke drank. En dat terwijl algemeen bekend is dat het primair gaat om de relatie tussen het gebruik van alcohol als carcinogene stof en het ontstaan van diverse ziekten waaronder kanker. Het kan niet zo zijn dat we als	

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	resultaat van uw rapport gaan zien dat de diverse soorten alcoholhoudende drank wat de risico's van het gebruik ervan betreft, tegen elkaar uitgespeeld worden. terwijl de kern is dat de alcohol die deze dranken bevatten als zodanig de belangrijkste factor die bepalend is voor de risico's. Ik vraag u tenminste een apart hoofdstuk te wijden aan de samenhang tussen de besproken ziekten en het gebruik van alcohol zonder daarbij onderscheid te maken tussen de diverse verschijningsvormen van alcohol. Dit mede gezien het feit dat er hoe langer hoe meer tussenproducten geconsumeerd worden, zoals Desperados (bier met Tequila), en Muscat (wijn met een scheutje gedistilleerde alcohol).	Factors in Breast Cancer) betreft het totale alcoholgebruik en niet het gebruik van bier, wijn of sterke drank. Daarom is deze publicatie niet toegevoegd in het achtergronddocument.[43] (Deze publicatie is verwerkt in het achtergronddocument Alcohol.) • De meta-analyse van Key e.a. blijft buiten beschouwing omdat daarin patiëntcontroleonderzoeken en cohortonderzoeken zijn samengevoegd.[44] De WCRF-publicatie over borstkanker[45] betreft het totale alcoholgebruik en niet het gebruik van bier, wijn of sterke drank. Daarom is deze publicatie niet toegevoegd in het achtergronddocument. (Deze publicatie is wel toegevoegd aan het achtergronddocument Alcohol.)
	Ik stuur u nogmaals het CUP rapport van het WCRF over borstkanker[45] en de twee zeer recente artikelen van studies die het verband tussen alcohol en borstkanker eenduidig aantonen[42,46].	Niet verwerkt: • De WCRF-publicatie over borstkanker[45] betreft het totale alcoholgebruik en niet het gebruik van bier, wijn of sterke drank. Daarom is deze publicatie niet toegevoegd in het achtergronddocument. (Deze publicatie is wel toegevoegd aan het achtergronddocument Alcohol.) • Cao e.a.[42] verscheen in juli 2015 en betreft analyses van resultaten van de twee afzonderlijke cohorten. Het is geen gepoolde analyse of meta-analyse. Deze publicatie valt buiten de periode van het literatuuronderzoek voor het achtergronddocument en wordt daarom niet meegenomen. • Romieu e.a.[46] (de 11-jaar follow-up van EPIC) presenteren geen analyses voor verbanden van het gebruik van bier, wijn of sterke drank met het risico op borstkanker en is daarom niet toegevoegd in het achtergronddocument over alcoholhoudende dranken. (Deze publicatie is wel toegevoegd aan het achtergronddocument Alcohol en vervangt daar de publicatie van Tjonneland e.a.[47] over de 6-jaar follow-up van EPIC.)
WKOF	1. Onderscheid tussen typen drank: De Gezondheidsraad maakt in haar onderzoek naar alcohol en kanker onderscheid tussen bier, wijn en sterke drank (regel 406-735). Het WCRF netwerk	Niet verwerkt De keuze om zowel een achtergronddocument Alcohol als een achtergronddocument Alcoholhoudende dranken op te stellen, vloeit voort uit de

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	evenals het International Agency for Research on Cancer (IARC) van de Wereldgezondheidsorganisatie maken echter geen onderscheid tussen verschillende soorten alcoholhoudende dranken omdat het verband tussen alcoholische dranken en kanker komt door ethanol, ongeacht welk type drank.[48,49] Het Wereld Kanker Onderzoek Fonds vraagt zich om deze reden af waarom de Gezondheidsraad ervoor heeft gekozen het onderzoek naar alcohol en kanker op te splitsen in verschillende soorten drank en adviseert om te kijken naar het verband tussen ethanol en kanker.	werkwijze van de commissie.[2] De integratie van deze bevindingen gebeurt niet in de achtergronddocumenten, maar in het advies.
WKOF	2. Darmkanker: De Gezondheidsraad ziet onvoldoende bewijskracht tussen alcohol uit sterke drank en het risico op darmkanker (regel 491-492). Het WCRF netwerk, evenals het IARC[48], ziet echter sterk wetenschappelijk bewijs voor een verband tussen alcohol en dikke darmkanker, ongeacht welk type alcoholische drank (RR 1.10 [1.06-1.13]).[50,51] Het WCRF netwerk schat dat per jaar 7% van de nieuwe gevallen van dikke darm- en endeldarmkanker in westerse landen voorkomen kan worden door geen alcohol te drinken.[52] Dit zijn jaarlijks in Nederland naar schatting meer dan 1000 gevallen van darmkanker. Alcohol wordt sinds 1988 door het IARC erkend als 'carcinogeen voor mensen' (indeling in Groep 1).[53] In 2007 heeft het IARC darmkanker toegevoegd als kankersoort die causaal gerelateerd is aan alcoholgebruik.[54] Helaas ontbreken beide toonaangevende bronnen het WCRF en het IARC in de bronnenlijst van het document van de Gezondheidsraad. Het Wereld Kanker Onderzoek Fonds verzoekt de Gezondheidsraad dan ook om deze wetenschappelijke informatie toe te voegen aan het achtergrond document.	Niet verwerkt De keuze om zowel een achtergronddocument Alcohol als een achtergronddocument Alcoholhoudende dranken op te stellen, vloeit voort uit de werkwijze van de commissie.[2] De commissie concludeert in het achtergronddocument Alcohol dat een alcoholgebruik van 30 tot 60 versus 0 gram per dag samenhangt met een ongeveer 20 procent hoger risico op darmkanker. De integratie van deze bevindingen gebeurt niet in de achtergronddocumenten, maar in het advies.
WKOF	3. Borstkanker: De Gezondheidsraad vindt geen eenduidig bewijs voor het verband tussen alcoholische dranken en borstkanker (regel 520-521, 524-525, 528-529). Uit een analyse van het WCRF netwerk is echter reeds sterk wetenschappelijk bewijs naar voren gekomen over het verband tussen alcohol en borstkanker bij vrouwen,	Niet verwerkt De keuze om zowel een achtergronddocument Alcohol als een achtergronddocument Alcoholhoudende dranken op te stellen, vloeit voort uit de werkwijze van de commissie.[2] De commissie concludeert in het achtergronddocument Alcohol dat een alcoholgebruik vanaf 10 gram versus 0 per

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	zowel premenopauzaal (RR 1.09 [1.01-1.17])[52] als postmenopauzaal (RR 1.08 [1.05-1.11]).[45,55] Tevens heeft het IARC in 2007/2010 de conclusie getrokken dat alcohol een risicofactor is voor borstkanker.[48] Het WCRF netwerk schat dat per jaar 22% van de nieuwe gevallen van borstkanker in westerse landen voorkomen kan worden door geen alcohol te drinken.[52] Dit zijn jaarlijks in Nederland ongeveer 3200 gevallen. Het Wereld Kanker Onderzoek Fonds adviseert de Gezondheidsraad om deze wetenschappelijke informatie toe te voegen aan het achtergrond document en de conclusie over alcohol en borstkanker te herzien.	dag hangt samen met een ongeveer 5% hoger risico op borstkanker bij vrouwen. De integratie van deze bevindingen gebeurt niet in de achtergronddocumenten, maar in het advies.
WKOF	4. Andere kankersoorten gerelateerd aan alcohol: Andere kankersoorten die een relatie hebben met alcohol zijn niet opgenomen in de top 10 ziekten die de Gezondheidsraad onder de loep heeft genomen en staan dan ook niet in het achtergronddocument. Echter, uit analyses van het WCRF netwerk is gebleken dat alcohol een significante risicofactor is voor mond-, keel- en strottenhoofd-kanker (RR 1.03 [1.02-1.04])[49], slokdarmkanker (RR 1.04 [1.03-1.05])[49] en leverkanker (RR 1.04 [1.02-1.06])[56]. Tevens is in een toonaangevende publicatie van het IARC uit 1988 reeds geconcludeerd dat alcohol het risico op deze kankersoorten significant verhoogt.[53] Het Wereld Kanker Onderzoek Fonds raadt daarom de Gezondheidsraad aan deze kankersoorten wel te benoemen in het achtergrond document over alcoholhoudende dranken. **Concluderend** Zowel het IARC als het WCRF netwerk zijn op basis van analyses van het bestaande onderzoek tot de conclusie gekomen dat er 7 soorten kanker causaal gerelateerd zijn aan alcohol, te weten: dikke darmkanker, borstkanker, mondkanker, keelkanker, strottenhoofdkanker, slokdarmkanker en leverkanker. Het verband tussen alcohol en kanker is onafhankelijk van het type drank en betreft ethanol. Het Wereld Kanker Onderzoek Fonds verzoekt de Gezondheidsraad deze informatie, gebaseerd op wereldwijd wetenschappelijk onderzoek, mee te nemen	Niet verwerkt Deze informatie over andere kankersoorten dan borstkanker, darmkanker en longkanker past niet bij de werkwijze die de commissie volgt bij het opstellen van de achtergronddocumenten.[2]

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	in de nieuwe Richtlijnen goede voeding 2015.	

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