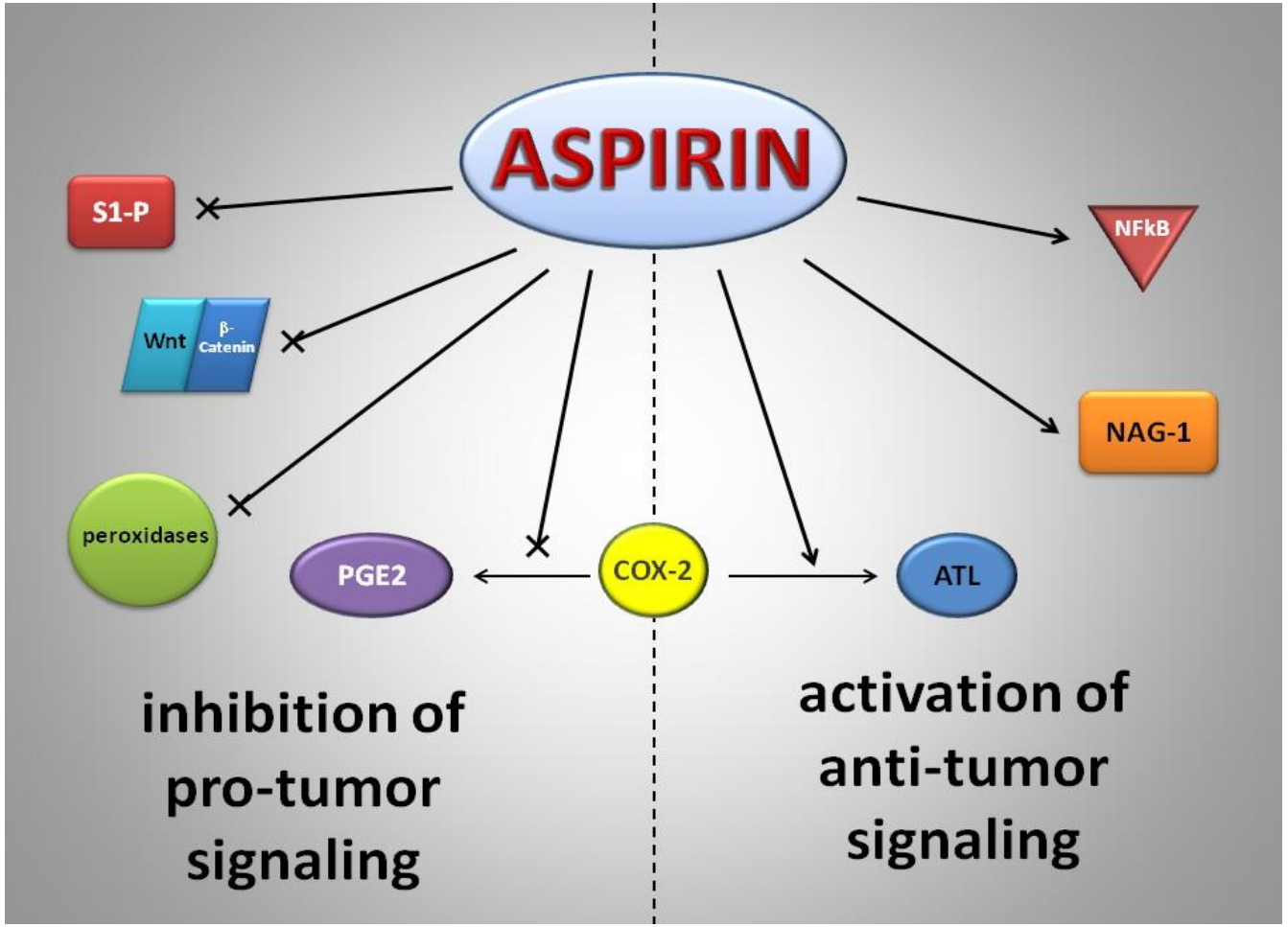
規律服用阿司匹林可降低罹患癌症及轉移的風險嗎?

報告人：湯梅芬

阿斯匹林 VS 癌症



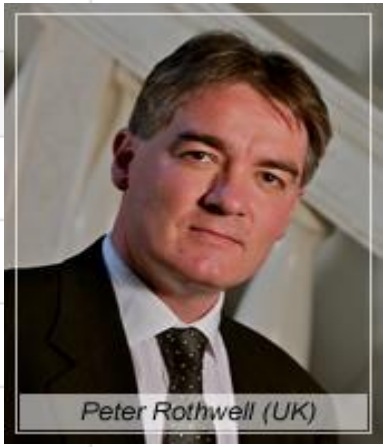
抑制促腫瘤信號的傳導　　激活抗腫瘤信號的傳導

Title：Effects of regular aspirin on long-term cancer incidence and metastasis : a systematic comparison of evidence from observational studies versus randomise trials .

Journal：Lancet Oncol. 2012 May;13(5):518-27.

Author ：Annemijn M Algra , Peter M Rothwell

Year	IF	Total Articles	Total Cites
2015/2016	26.509	-	30800
2014	24.690	169	24861
2013	24.725	163	20565
2012	25.117	153	17005
2011	22.589	105	13237
2010	17.764	108	10852


Peter Rothwell (UK)

步驟一：
系統性文獻回顧探討的問題為何？(PICO)

步驟 1	系統性文獻回顧探討的問題為何？（PICO)
Population/ Problem	Cancer patient (colorectal cancer and several other cancers)
Intervention	Regular use Aspirin or Aspirin plus other NSAIDs
Comparison	No Aspirin use
Outcomes	①Cancer incidence ②Risk of metastasis

步驟二：
系統性文獻回顧的品質如何？(FAITH)

F—研究是否找到（Find）所有的相關證據？

良好的文獻搜尋**至少應包括二個主要的資料庫**(如：Medline, Cochrane 考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時**使用 MeSH 字串**及一般檢索詞彙(text words)。

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Methods

Search strategy and selection criteria

We aimed to identify published observational studies of the association between use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and risk of all types of cancer. We searched PubMed, National Library of Medicine, from Jan 1, 1950, to Jan 15, 2011, with the following search terms: ("neoplasms"[MeSH Terms] OR cancer[Text word]) AND (aspirin OR salicyl* OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR "anti-inflammatory agents, non-steroidal" [Pharmacological Action] OR NSAID[Text Word]). Reference lists of all retrieved articles and previous systematic reviews were checked for further eligible publications.

評讀結果：∨是□否□不清楚

PRISMA

Results

We identified 13 728 articles with our electronic search (figure 1). Review of titles and abstracts identified 323 potentially eligible studies, of which 148 were found to report original data on review of the full papers. We found an additional 160 papers after checking review articles, reference lists, and other sources. Of these 308 articles, 60 were duplicates or were otherwise ineligible. Of the 248 reports remaining, 187 described a total of 150 case–control studies and 61 described 45 cohort studies (figure 1). Details of these studies are shown in the appendix (pp 4–46, 68–82) along with details of studies that were excluded at full-paper stage (appendix pp 66–67, 84–86). Details of the randomised trials are also shown in the appendix (pp 65, 83). Eligible case–control studies included 141 577 participants with cancer and there were 41 575 cancers during 39 981 678 person-years of follow-up in eligible cohort studies.

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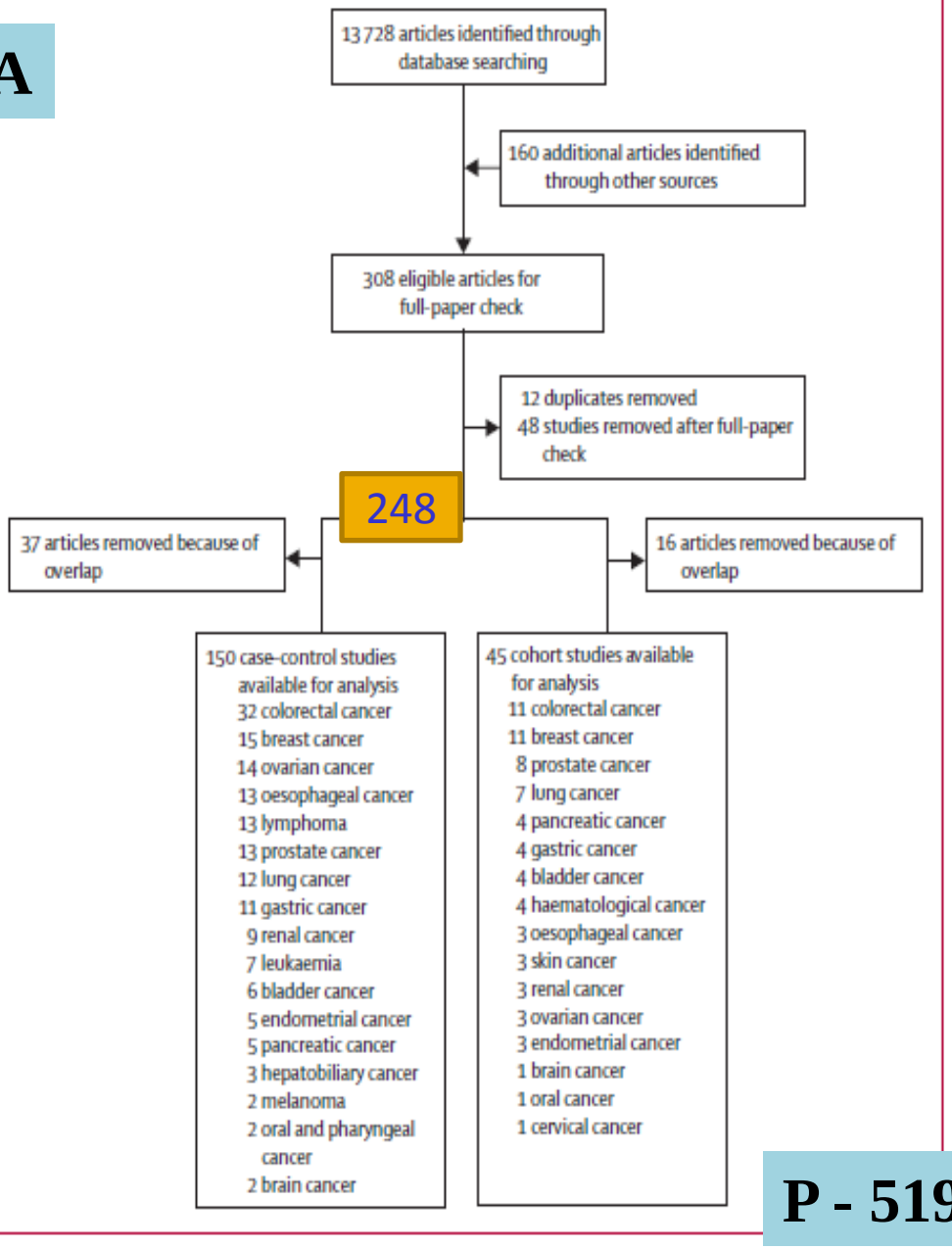

Figure 1: Studies included and excluded

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A－文獻是否經過嚴格評讀（Appraisal）？ -2

應根據不同臨床問題的文章類型，**選擇適合的評讀工具**，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)。

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Methods

Papers were eligible for inclusion if they reported results of case–control and cohort studies of use of aspirin or NSAIDs and risk of cancer. We excluded studies done in populations with specific precancerous diseases (eg, polyposis coli). Eligibility was restricted to studies in man, but had no language restriction. In case of multiple publications from one study population, data relating to the largest number of cancer cases were extracted and included in the analysis, unless more detailed exposure data were reported in another paper. For each study, we extracted data for setting, population (population-based or hospital-based, size, age, sex), definition of use (including stratification by frequency, dose, or duration of use), diagnostic criteria for cancer, case-finding methods, assessment of exposure and control, and any matching factors (age, sex, or other potential confounders). When necessary, authors were contacted and additional unpublished data were requested.

Inclusion of randomised trials has been reported previously for analysis of the effect of aspirin on long-term risk of death due to cancer,[13] and the analysis of effects on risk of metastasis.[16] Briefly, eligibility required randomisation to aspirin versus no aspirin and a mean scheduled duration of trial treatment of 4 years or more. Individual patient data for all in-trial cancer deaths (coded by the ninth and tenth revisions of the International Classification of Diseases) were obtained from seven trials.[13] Additionally, in three UK trials,[22-24] cancer deaths

評讀結果：□是□否∨不清楚

I－是否只納入（included）具良好效度的文章？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是**極小偏誤的試驗**。

Methods

Search strategy and selection criteria

We aimed to identify published observational studies of the association between use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and risk of all types of cancer. We searched PubMed, National Library of Medicine, from Jan 1, 1950, to Jan 15, 2011, with the following search terms: ("neoplasms"[MeSH Terms] OR cancer[Text word]) AND (aspirin OR salicyl* OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR "anti-inflammatory agents, non-steroidal" [Pharmacological Action] OR NSAID[Text Word]). Reference lists of all retrieved articles and previous systematic reviews were checked for further eligible publications.

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評讀結果：∨是□否□不清楚

T—作者是否以表格和圖表「總結」（total up）試驗結果？

應該用**至少 1 個摘要表格呈現所納入的試驗結果**。若結果相近，可針對結果進行**統合分析**(meta-analysis)，並以「**森林圖**」(forest plot)呈現研究結果，最好再加上**異質性分析**（見後文）。

Study type	N	Aspirin	Controls	OR (95% CI)	Significance	Heterogeneity
Randomised trials						
Daily aspirin	6	91/9833	154/9859	0·58 (0·44-0·78)	p=0·0002	p=0·45
Daily aspirin ≥5 years	6	74/8034	134/8012	0·55 (0·41-0·76)	p=0·0002	p=0·26

	N	Cases	Controls	OR (95% CI)	Significance	Heterogeneity
Case-control						
Any aspirin	26	10464/25618	28300/47834	0·67 (0·60-0·74)	p<0·0001	p<0·0001
Maximum reported aspirin	17	1551/12659	2664/18153	0·62 (0·58-0·67)	p<0·0001	p=0·13
Aspirin ≥5 years	10	971/7682	1534/10029	0·68 (0·63-0·75)	p<0·0001	p=0·82
Daily aspirin	4	165/1254	349/1523	0·49 (0·40-0·60)	p<0·0001	p=0·65
Daily aspirin ≥5 years	1	66/1668	121/1973	0·63 (0·46-0·86)	p=0·004	NA

	N	Aspirin	Controls	RR (95% CI)	Significance	Heterogeneity

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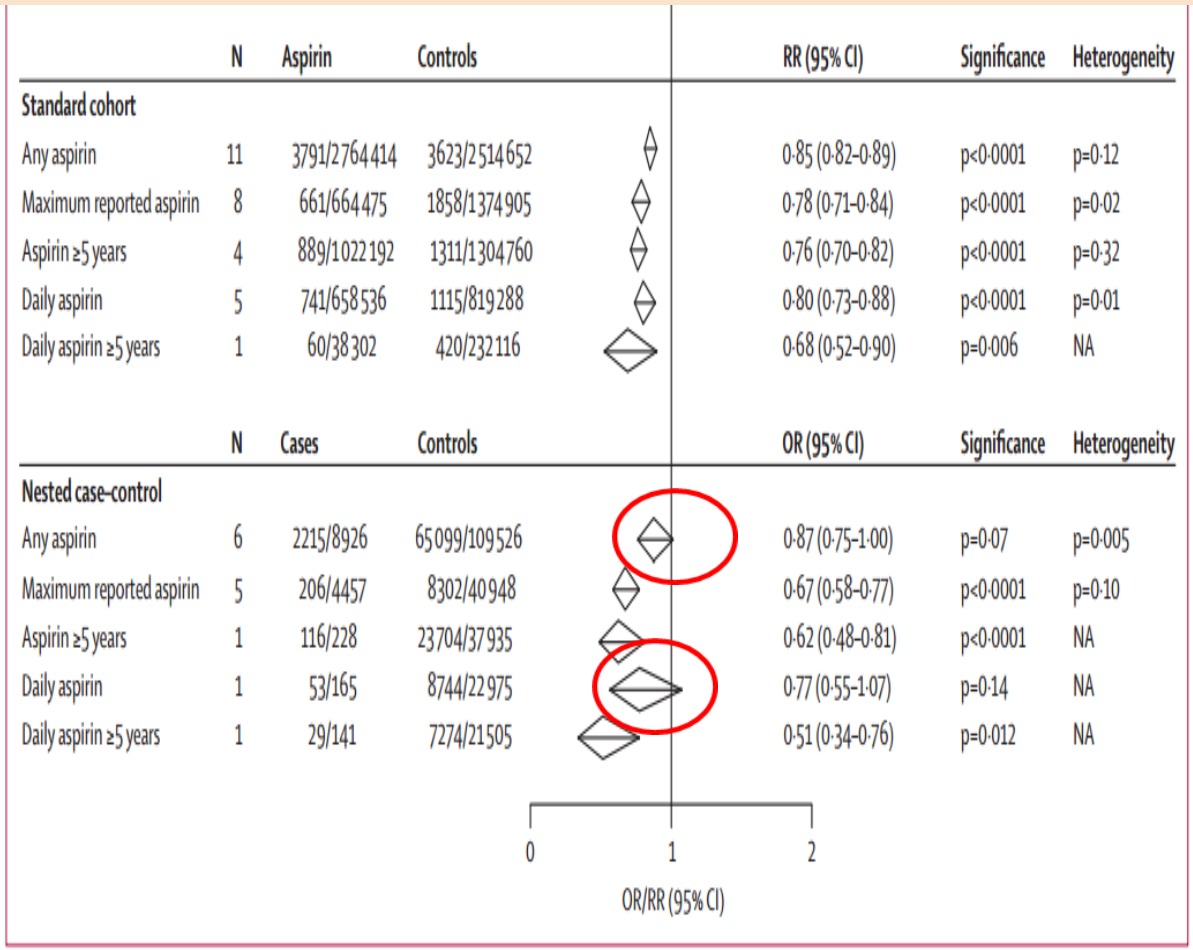

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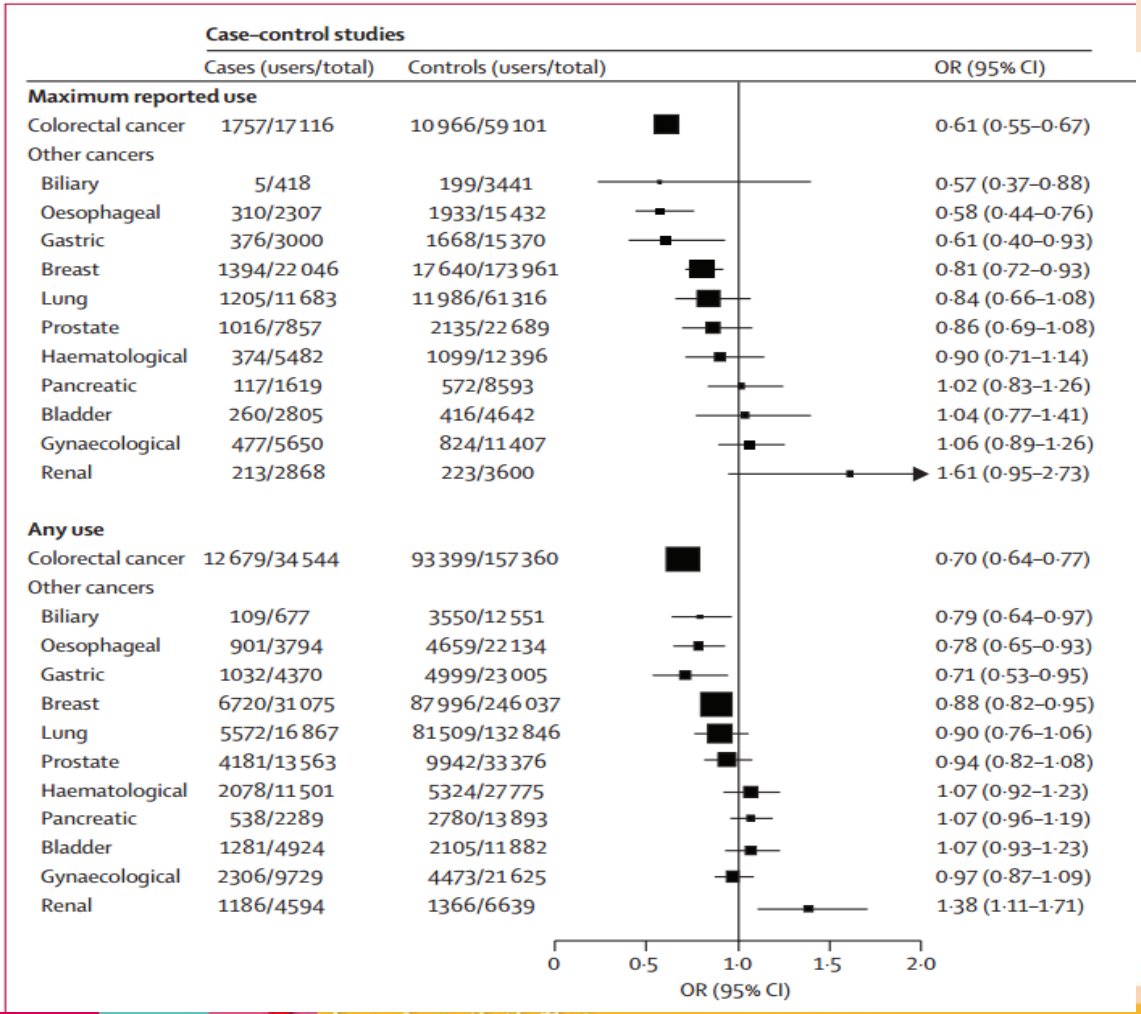

Case–control studies	Cases (users/total)	Controls (users/total)	OR (95% CI)
Maximum reported use			
Colorectal cancer	1757/17 116	10 966/59 101	0·61 (0·55–0·67)
Other cancers			
Biliary	5/418	199/3441	0·57 (0·37–0·88)
Oesophageal	310/2307	1933/15 432	0·58 (0·44–0·76)
Gastric	376/3000	1668/15 370	0·61 (0·40–0·93)
Breast	1394/22 046	17 640/173 961	0·81 (0·72–0·93)
Lung	1205/11 683	11 986/61 316	0·84 (0·66–1·08)
Prostate	1016/7857	2135/22 689	0·86 (0·69–1·08)
Haematological	374/5482	1099/12 396	0·90 (0·71–1·14)
Pancreatic	117/1619	572/8593	1·02 (0·83–1·26)
Bladder	260/2805	416/4642	1·04 (0·77–1·41)
Gynaecological	477/5650	824/11 407	1·06 (0·89–1·26)
Renal	213/2868	223/3600	1·61 (0·95–2·73)
Any use			
Colorectal cancer	12 679/34 544	93 399/157 360	0·70 (0·64–0·77)
Other cancers			
Biliary	109/677	3550/12 551	0·79 (0·64–0·97)
Oesophageal	901/3794	4659/22 134	0·78 (0·65–0·93)
Gastric	1032/4370	4999/23 005	0·71 (0·53–0·95)
Breast	6720/31 075	87 996/246 037	0·88 (0·82–0·95)
Lung	5572/16 867	81 509/132 846	0·90 (0·76–1·06)
Prostate	4181/13 563	9942/33 376	0·94 (0·82–1·08)
Haematological	2078/11 501	5324/27 775	1·07 (0·92–1·23)
Pancreatic	538/2289	2780/13 893	1·07 (0·96–1·19)
Bladder	1281/4924	2105/11 882	1·07 (0·93–1·23)
Gynaecological	2306/9729	4473/21 625	0·97 (0·87–1·09)
Renal	1186/4594	1366/6639	1·38 (1·11–1·71)

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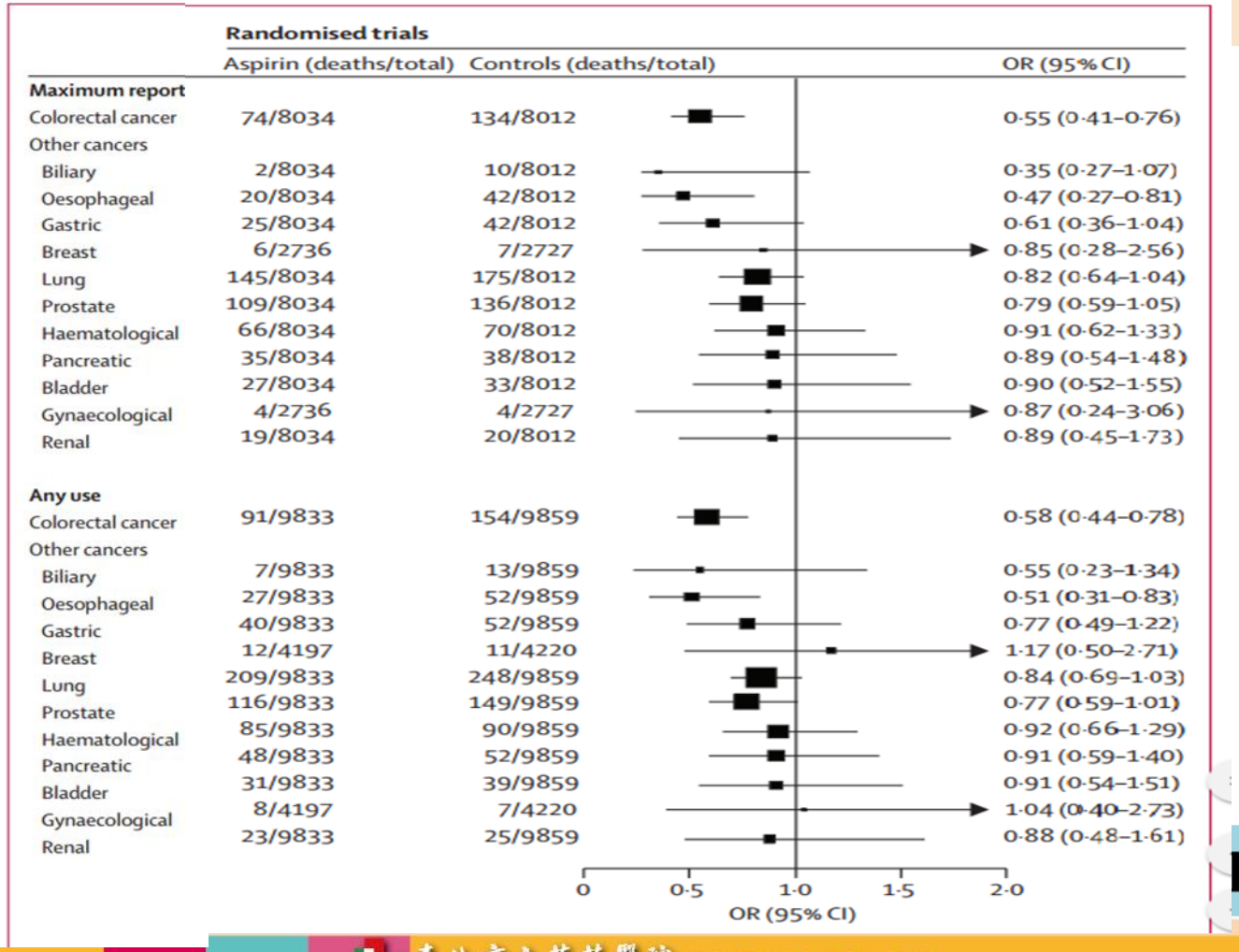

P - 521

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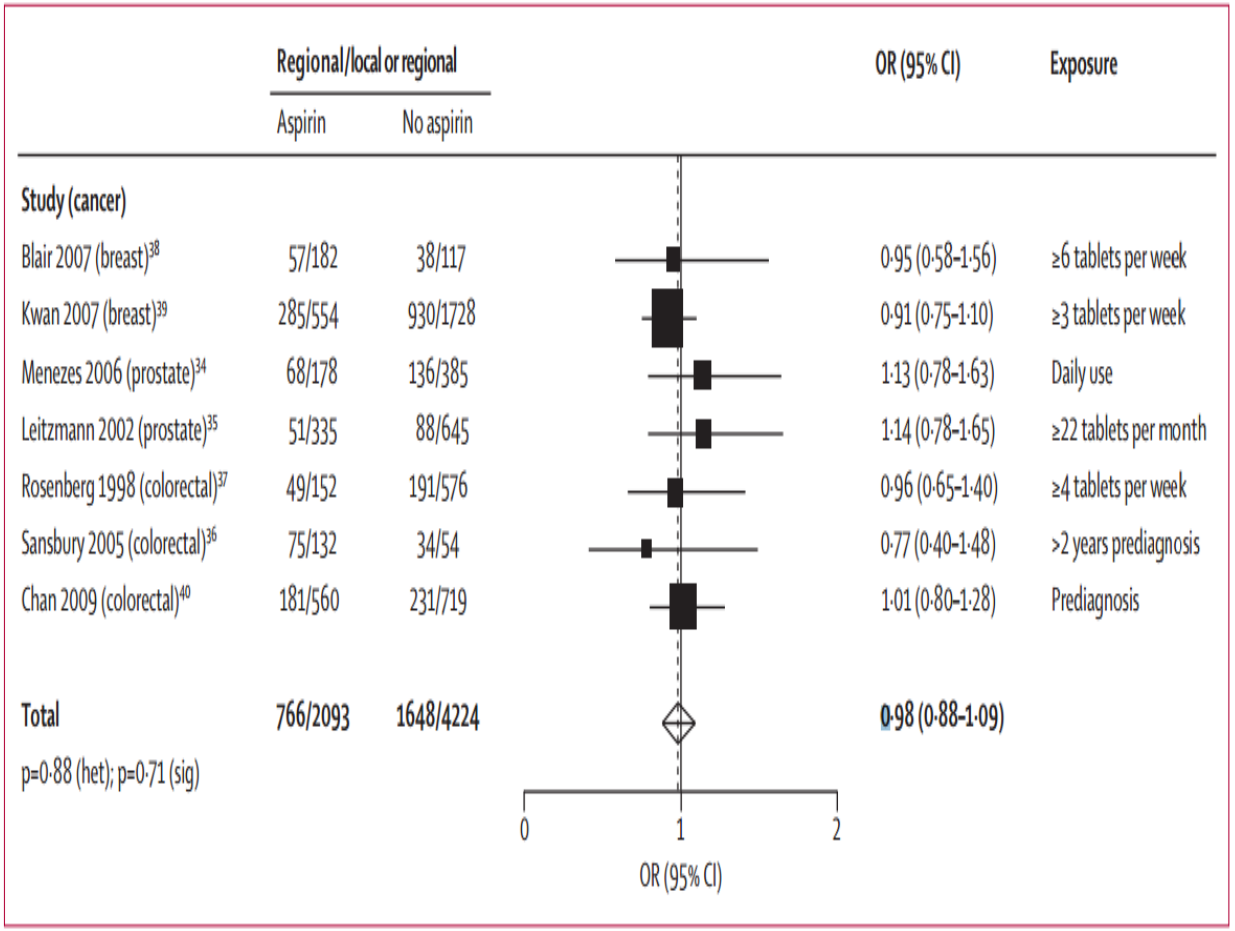

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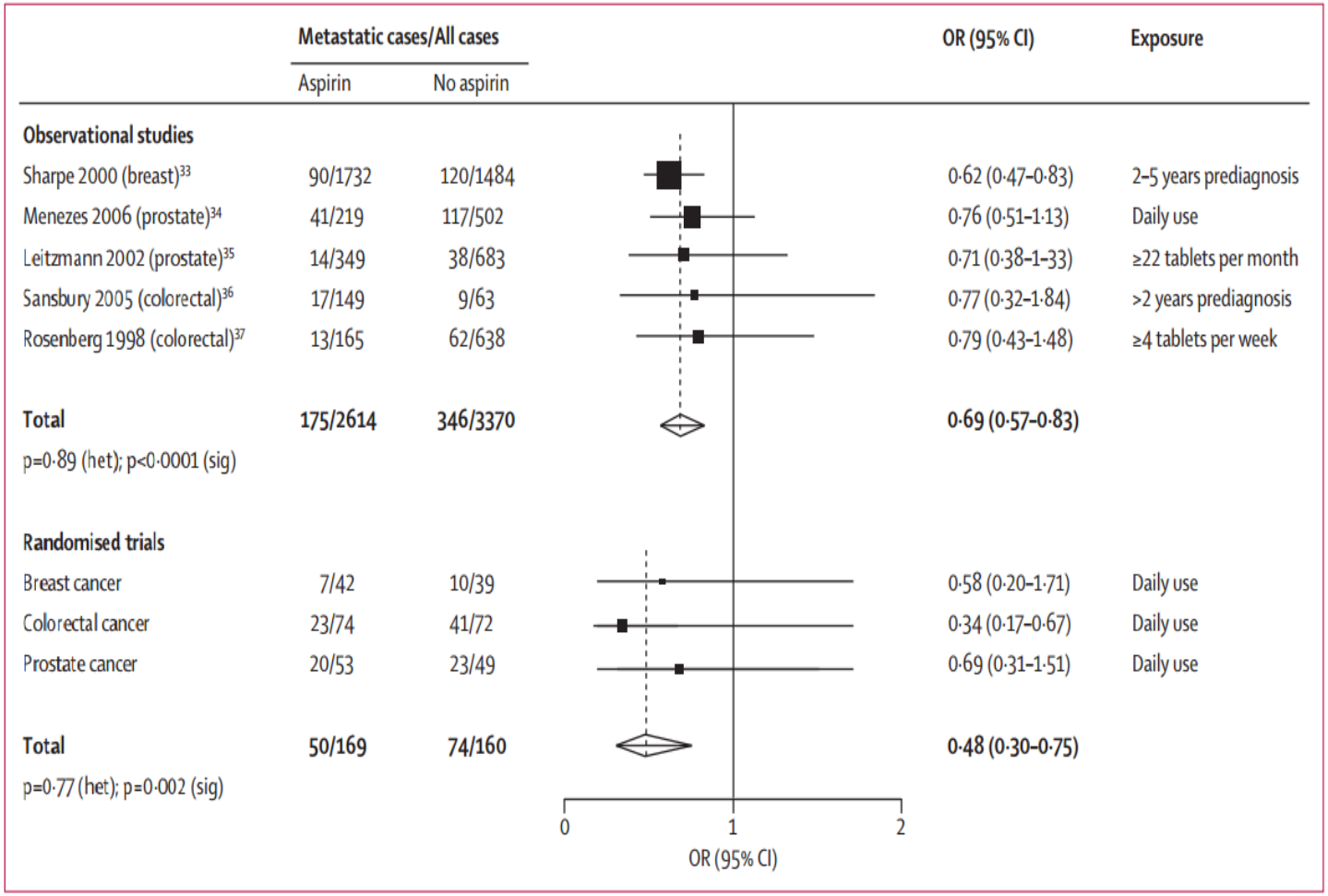

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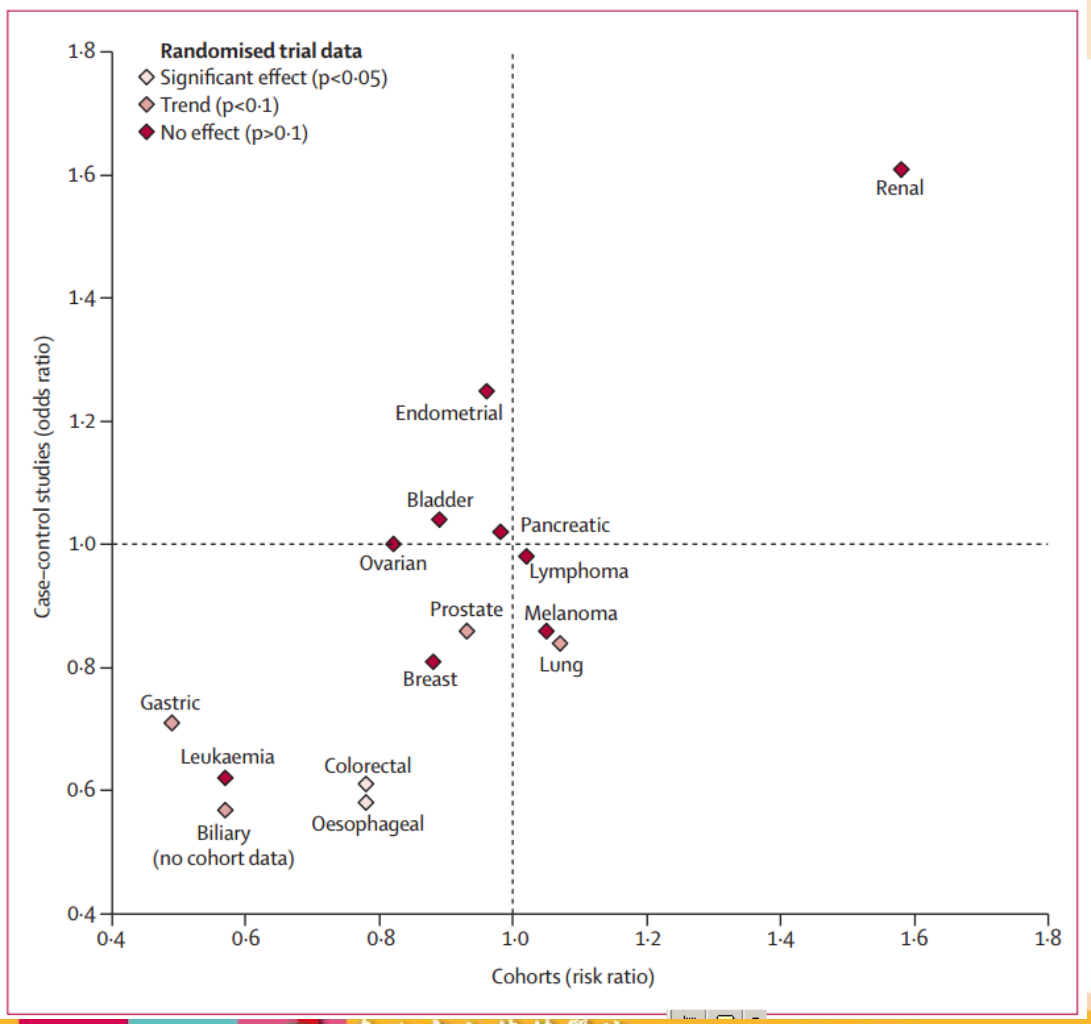

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H－試驗的結果是否相近－異質性(Heterogeneity)？

在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的 PICO 及研究方法，探討造成**異質性**的原因。

Study type	N	Aspirin	Controls	OR (95% CI)	Significance	Heterogeneity
Randomised trials						
Daily aspirin	6	91/9833	154/9859	0·58 (0·44–0·78)	p=0·0002	p=0·15
Daily aspirin ≥5 years	6	74/8034	134/8012	0·55 (0·41–0·76)	p=0·0002	p=0·26
	N	**Cases**	**Controls**	**OR (95% CI)**	**Significance**	**Heterogeneity**
Case–control						
Any aspirin	26	10 464/25 618	28 300/47 834	0·67 (0·60–0·74)	p<0·0001	p<0·0001
Maximum reported aspirin	17	1551/12 659	2664/18 153	0·62 (0·58–0·67)	p<0·0001	p=0·13
Aspirin ≥5 years	10	971/7682	1534/10 029	0·68 (0·63–0·75)	p<0·0001	p=0·82
Daily aspirin	4	165/1254	349/1523	0·49 (0·40–0·60)	p<0·0001	p=0·65
Daily aspirin ≥5 years	1	66/1668	121/1973	0·63 (0·46–0·86)	p=0·004	NA
	N	**Aspirin**	**Controls**	**RR (95% CI)**	**Significance**	**Heterogeneity**
Standard cohort						
Any aspirin	11	3791/2 764 414	3623/2 514 652	0·85 (0·82–0·89)	p<0·0001	p=0·12
Maximum reported aspirin	8	661/664 475	1858/1 374 905	0·78 (0·71–0·84)	p<0·0001	p=0·02
Aspirin ≥5 years	4	889/1 022 192	1311/1 304 760	0·76 (0·70–0·82)	p<0·0001	p=0·32
Daily aspirin	5	741/658 536	1115/819 288	0·80 (0·73–0·88)	p<0·0001	p=0·01
Daily aspirin ≥5 years	1	60/38 302	420/232 116	0·68 (0·52–0·90)	p=0·006	NA
	N	**Cases**	**Controls**	**OR (95% CI)**	**Significance**	**Heterogeneity**
Nested case–control						
Any aspirin	6	2215/8926	65 099/109 526	0·87 (0·75–1·00)	p=0·07	p=0·005
Maximum reported aspirin	5	206/4457	8302/40 948	0·67 (0·58–0·77)	p<0·0001	p=0·10
Aspirin ≥5 years	1	116/228	23 704/37 935	0·62 (0·48–0·81)	p<0·0001	NA
Daily aspirin	1	53/165	8744/22 975	0·77 (0·55–1·07)	p=0·14	NA
Daily aspirin ≥5 years	1	29/141	7274/21 505	0·51 (0·34–0·76)	p=0·012	NA

1 2

(95% CI)

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評讀結果：∨是□否□不清楚

結果為何？

使用何種評估方式，療效有多大（是否來自隨機效果）？

➢Case–control studies：

1. 規律使用Aspirin與降低罹患**結直腸癌**的風險有相關性（P<0.0001）。
2. 規律使用Aspirin與降低**白血病**的風險有相關性

➢Randomise studies：

每天服用Aspirin可降低罹患直結腸癌**20年**的死亡風險。

結果為何？

使用何種評估方式，療效有多大（是否來自隨機效果）？

➢Cohort studies：

1. 以服用Aspirin的**頻率**及**期間**進行分層分析，亦得到上述相似的結果。
2. Aspirin也被認為可以降低其他**腸胃道癌症**(食道、胃、膽管)和**乳腺癌**的罹癌風險。

結果為何？

使用何種評估方式，療效有多大（是否來自隨機效果）？

➢Observation studies：

1. 少數的研究，以癌症診斷期別進行分層分析，結果顯示定期服用Aspirin與降低癌症**遠端轉移**有相關性(P<0.0001)，但對於**近端區域**的擴散，並無法降低(P=0.71)。
2. 經常服用Aspirin可降低**多種癌症**的長期風險和遠處轉移的風險。

結果為何？

使用何種評估方式，療效有多大（是否來自隨機效果）？

- **每日**服用或至少一週服用**3-6次**阿斯匹林，治療的效果最大。
- 長期追蹤服用低劑量阿斯匹林病人，**直腸癌**比結腸癌有**更大**治療效果。
- 長期服用低劑量阿斯匹林，並搭配**乙狀結腸鏡**檢查，或許可大幅降低大腸與直腸等相關部位的癌症發病率。
- 低劑量阿斯匹林至少治療**五年**以後，才會有顯著的療效。(Low dose：75mg/day or ＜300mg/day)

Question

◆您贊成每日服用低劑量Aspirin

降低罹患腸胃道癌症的風險嗎？

Journal Club [72]@Wanfang hospital
2016.07.05.

綠(同意，低劑量/5年) 1人

黃(懷疑，需再評估) 27人

紅(不同意) 8人

謝謝聆聽