

Quality of systematic reviews used in guidelines for oncology practice

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Background: Systematic reviews are an important tool for developing clinical recommendations. Those of high quality assure a good level of confidence on the strength of the recommendations.

Methods: A QUOROM-based checklist was applied to the reviews cited in a sample of guidelines on breast and colon cancer prevention and therapy. The checklist provided a weight for each criterion and a total quality score. Each review was independently evaluated by two reviewers; disagreements were solved by consensus.

Results: Eighty reviews (96%) were retrieved and evaluated; 36 focused on breast, and 44 on colorectal cancer. Twenty-three reviews (29%) did not match the definition of systematic review. In 17 (21%) the searching methods were unclear or described elsewhere. Forty (50%) were systematic. Not systematic, low and very low quality reviews accounted for 70% of the total. No review obtained the A+ class score; only 5 (6%) the A– and 7 (9%) the B+.

Conclusions: The results of this assessment provide a sober picture of the quality of the sources used to build guidelines. Oncologists should be aware that they could be relying on poor underlying documents. Writing groups should be aware of methodological problems, and should consult the existing manuals for the preparation of guidelines.

Key words: breast cancer, colorectal cancer, evidence-based medicine, guidelines, quality assessment, reviews

introduction

Methods for grading clinical evidence and recommendations are a relatively new and important area of research. Systematic reviews and guidelines provide essential information for making well informed decisions. Implicitly or explicitly, reviewers and people who use reviews draw conclusions about the quality of evidence, and such judgments guide subsequent decisions.

Assessing the quality of evidence appears very important; however, until few years ago there was wide variation in the approaches used to grade evidence and recommendations by different organisations and all of these approaches had important shortcomings.

Systematic and explicit approaches help to protect against errors, resolve disagreements, facilitate critical appraisal, and communicate the conclusions. Agreement on methodological approaches for the evaluation of the evidence has been reached by the GRADE working group in 2004 [6]; they developed a method to make sequential judgements about the quality of evidence for each important outcome, the overall quality of evidence across outcomes, and the recommendations. Some practical tools have been developed for assessing the quality

of review articles [10, 11] and for evaluating the quality of reporting [8].

Our main objective was to assess the quality of the sources (reviews, systematic reviews and meta-analyses) used for the development of guidelines on prevention and treatment of breast and colorectal cancers.

methods

Reviews and meta-analysis used for the development of guidelines on prevention and treatment of breast and colorectal cancers published between 1998 and 2003 have been identified, retrieved and evaluated using a quality checklist.

identification of guidelines

To identify the guidelines focused on prevention and treatment of cancers under study, the websites of some of the main international institutions involved with prevention and treatment of cancer were explored. The following websites were checked:

- NHMRC (National Health and Medical Research Council), Australia
- Cancer Care Ontario Practice Guidelines Initiative
- NCCN (National Comprehensive Cancer Network)
- SIGN (Scottish Intercollegiate Guidelines Network)
- ASCO (American Society of Clinical Oncology)

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- ESMO (European Society for Medical Oncology)
- American College of Gastroenterology
- NCI (National Cancer Institute)
- Royal College of Surgeons of England; Association of Coloproctology of Great Britain and Ireland
- Royal College of Radiologists Clinical Oncology Information Network
- COR-CPO, Piedmont Region

From these websites, guidelines on primary prevention and treatment (including clinical follow-up of patients) of breast and colorectal cancer published from 1998 to 2003 were identified and downloaded. Secondary prevention was excluded. The search was performed between October and December 2003.

identification of reviews

Text and references of the retrieved guidelines were scanned to identify all possible reviews used as source of information for the elaboration of the recommendations, as well as other possible guidelines of interest. Reviews focused on adverse effects, treatment of complications, and quality of life were excluded.

Using a formal definition of systematic review (e.g. [4]), the number of papers meeting the definition should have been very small. For this reason we used a less strict definition to classify the retrieved papers: systematic reviews were considered all those performing a literature search at least on an electronic scientific database (e.g. Medline).

On this base, the reviews were classified as:

- Clearly systematic
- Doubtful (for unclear searching methods or because searching methods were described elsewhere)
- Not systematic

QUOROM-based checklist

In order to assess the quality of the reviews, several checklists were examined: the Oxman-Guyatt index [11], the QUOROM [8], that used by the New Zealand Guidelines Group [9] and that used by the Scottish Intercollegiate Guidelines Network [12]. Among these, the most validated are the Oxman-Guyatt index, consisting of 10 general criteria, and the QUOROM, consisting of 21 headings focused on the quality of reporting. The QUOROM was judged as the most comprehensive one, but to use it as a tool to evaluate the quality of the reviews, the following criteria were added to the original checklist:

- **Title:** the identification of the study design and the intervention under study.
- **Abstract:** the description of results of the heterogeneity assessment (Cochrane Collaboration: [7]).
- **Objectives:** a clear description of the review's objectives, including intervention, comparison and outcome definitions [9, 12].
- **Methods:** the completeness of the bibliographic sources; the language exclusions; the update of the searching; the duplicate assessment for the selection procedure, the quality assessment and the data abstraction [11, 12]; the inclusion of allocation concealment, blinding, attrition and ITT (intention-to-treat analysis) among the criteria for assessing the quality of the trials. For non randomised studies, a similar list was

developed, containing description of population base, attrition, and control for confounding variables.

- **Results:** in the 'studies characteristics' section a list of the outcomes measured by each included study; a list of excluded studies and the reasons for the exclusion [3]. Subgroup analysis, results of the heterogeneity assessment, assurance of homogeneity in combining studies in the meta-analysis were also considered as quality criteria [11, 12]. Formal evaluation of publication bias is very rare, so that a clear description of the results (providing funnel plot or the findings of other methods) was added as a quality criterion [3].
- **Discussion:** recommendations for practice.

The comparison between the original QUOROM checklist and the modified version is available on request.

quality scores

The QUOROM-based checklist (Table 1) provides a value for each quality criterion whose total score is 50.

A score was assigned if a specific criterion was completely satisfied; for the title, abstract, introduction and objectives sections a score was given only if the information was described in the specific section. As regards methods and results, the procedure was less strict: the score was given also when the information was not in the proper section, but was provided somewhere.

For the search strategy, a score was given if at least the keywords used to retrieve the papers were provided.

For the quality assessment additional criteria, the score was attributed if the review used at least three of the four mentioned criteria in the methods section.

Sensitivity analysis was considered as the analysis performed with and without low quality studies; all the others were considered as subgroup analyses.

The QUOROM-based checklist is fully presented in Table 1.

Four quality classes were created, based on the completion of the total score (A, B, C, D); each class was further divided into two (+ and -). Therefore, according to the scores, seven classes were finally created: A+: 46-50; A-: 41-45; B+: 36-40; B-: 31-35; C+: 26-30; C-: 21-25; D: 0-20.

Such categories can be referred to the definitions developed by the GRADE working group [6].

- High (A+, A-): Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate (B+, B-): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low (C+, C-): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low (D): Any estimate of effect is very uncertain.

quality assessment

Each systematic review was independently evaluated by two reviewers, using the QUOROM-based checklist. Disagreements were solved by consensus.

Table 1. QUOROM-based check-list for quality assessment

Heading	Descriptor	Weight	Value
Title:		2.5	
review	Identify the report as a meta-analysis or systematic review		1.00
study design	Identify the kind of studies included (RCT, etc)		0.75
intervention	Identify the intervention		0.75
Abstract:		5.0	
format	Use a structured format		0.50
objectives	Describe the intervention/ studied relationship		0.35
	Describe the comparison		0.35
	Describe the outcome		0.30
data sources	Describe databases and other sources used		0.70
	Describe the years covered		0.30
methods	Define the population		0.12
	Define the intervention		0.12
	Define the control group		0.12
	Define the outcomes		0.12
	Define the study design		0.12
	Describe the quality assessment methods		0.20
	Describe the quantitative data synthesis methods		0.20
results	Describe number of included studies		0.20
	Describe number of excluded studies		0.20
	Describe quantitative findings		0.20
	Describe subgroups analysis		0.20
	Describe heterogeneity of results		0.20
conclusion	Describe the main conclusion		0.50
Introduction:		2.5	
problem	Describe the clinical problem		0.75
intervention	Describe biological rationale for the intervention		0.75
review	Describe rationale for the review		1.00
Objectives:		5.0	
intervention	Definition of experimental intervention/studied relationship		2.00
control	Definition of control intervention		1.50
outcome	Definition of outcome measures		1.50
Methods:		15.0	
searching	Describe searching strategy		0.50
	Describe databases and other sources used		0.50
	Describe years covered		0.50
	Describe any language exclusion		0.50
	Use at least two bibliographic sources		0.50
	Update to less than 2 years before publication		0.50
	Include at least two languages		0.50
selection	Describe inclusion criteria		0.75
	Describe exclusion criteria		0.75
	Define population		0.25
	Define intervention/studied relationship		0.25
	Define control		0.25

Table 1. (Continued)

Heading	Descriptor	Weight	Value
	Define outcomes		0.25
	Define study design		0.25
	Use of duplicate assessment		0.75
quality	Description of quality assessment method		0.75
	List of quality assessment criteria		0.75
	Concealment, blinding, attrition and ITT as quality criteria		0.75
	Use of duplicate assessment		0.75
data abstraction	Description of data abstraction method		1.00
	Use of duplicate assessment		1.00
quantitative	Describe measure of effects		0.50
data synthesis	Describe method of combining results		0.50
	Describe handling of publication bias		0.50
	Describe method for assessing heterogeneity		0.50
	Describe a priori sensitivity analysis		0.50
	Describe any subgroup analysis		0.50
Results:		13.0	
Studies	Describe the characteristics of the population		0.50
characteristics	Describe the sample size		0.50
	Describe the intervention		0.50
	Describe the control		0.50
	Describe the study design		0.50
	Describe measured outcomes		0.50
	Describe follow-up period		0.50
excluded	List of excluded studies		1.00
studies	Description of reasons for exclusion		1.00
quality	Description of quality assessment findings		1.50
quantitative	Present simple summary results		0.75
data synthesis	Perform sensitivity analysis		0.75
	Perform subgroup analysis		0.75
	Assess heterogeneity		0.75
	Provide meta-analysis or synthetic table of results		0.75
	Data are included in meta-analysis on ITT basis		0.75
	Combine studies in meta-analysis only if homogeneous		0.75
	Provide funnel plot assessing publication bias		0.75
Discussion:		7.0	
results	Summarize key findings		1.50
validity	Discuss internal quality of the studies		0.75
	Discuss external validity of the studies/heterogeneity		0.75
	Discuss potential bias in the review process		0.50
interpretation	Interpretation of results		2.50
recommendations	Suggest future research needed		0.50
	Suggest public health/practice recommendations		0.50

The findings were analysed in order to obtain summary results. Only the summary of the assessment is provided in this report; however, the result of each assessment is available on request.

Based on the quality of the reviews cited by each Guideline, a general evaluation of the source of evidence used to build practice recommendations was given.

Lastly, recommendations were elaborated for the improvement of systematic reviews and the guidelines development.

results

The flow of articles evaluated through the exercise is shown in Figure 1.

guidelines

Out of 128 guidelines published between 1998 and 2003 and identified by the search, 59 guidelines focused on primary prevention and treatment of breast ($n = 33$) and colon cancer ($n = 23$) or on both cancer sites ($n = 3$) were downloaded and examined (Guidelines: [GL1–59]) (Table 2). As regards year of publication, four (6.8%) were published in 1998, five (8.5%) in 1999, seven (11.9%) in 2000, 12 (20.3%) in 2001, 11 (18.6%) in 2002, and 20 (33.9%) in 2003.

reviews cited in the guidelines

Overall, 171 reviews were cited by the 59 guidelines. Out of the 83 reviews focused on breast and colon cancer prevention or treatment, 80 (96.4%) were retrieved and evaluated (breast cancer $n = 36$, colorectal cancer $n = 44$); three reviews [R15,

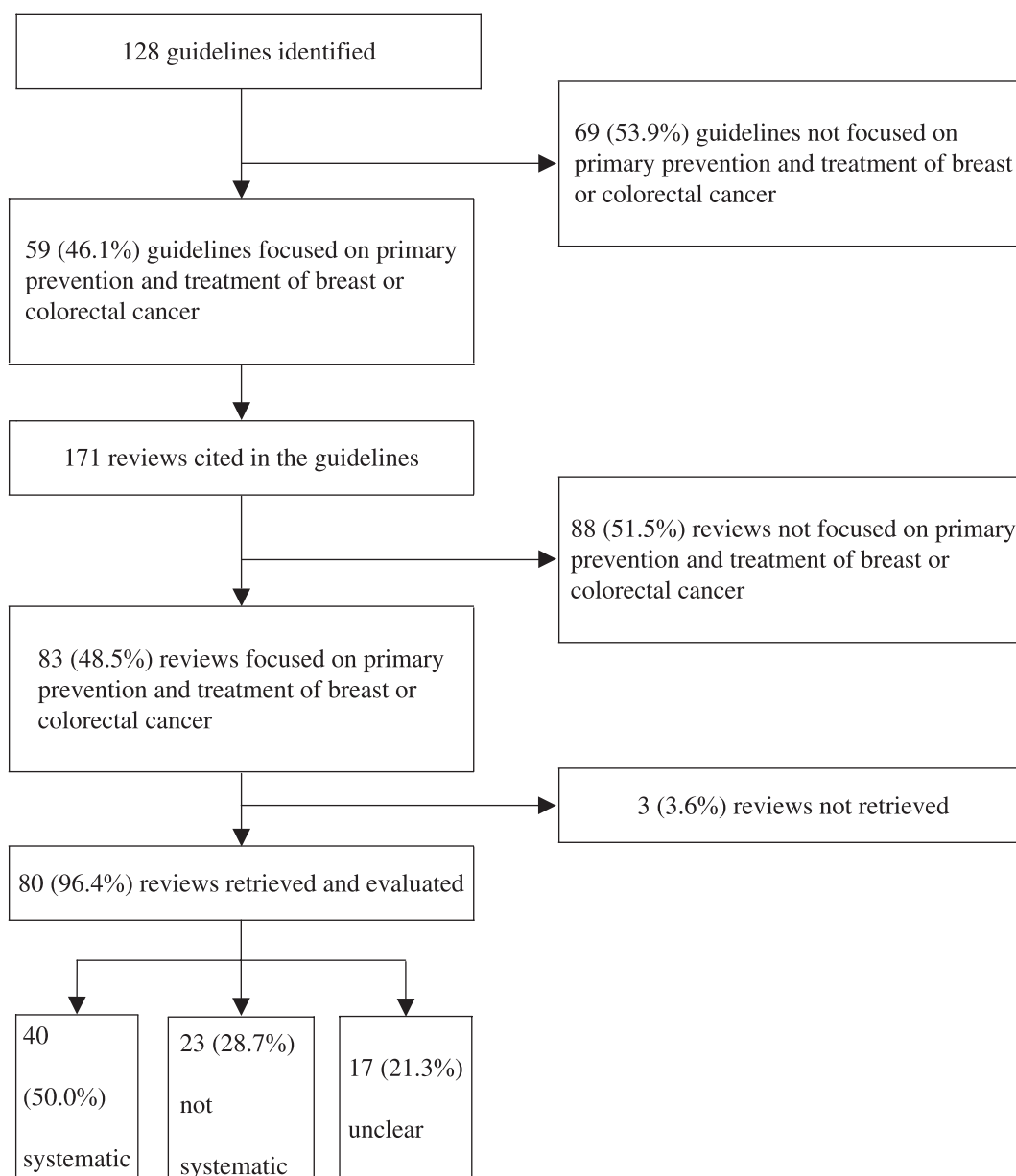


Figure 1. Flow diagram of the reviews under analysis

Table 2. Guidelines (GL) for prevention and treatment of breast and colon cancer by international institution and cancer site

International institution	Breast Cancer	Colon Cancer	Both cancers	Total	Reference
NHMRC	3	1	1	5	GL30–GL34
Cancer Care Ontario Practice Guideline Initiative	19	8	0	27	GL4–GL9, GL12, GL17–GL26, GL28–GL29, GL44–GL45, GL49, GL54–GL58
NCCN	3	3	0	6	GL35–GL40
SIGN	1	1	1	3	GL50–GL52
ASCO	3	1	1	5	GL1, GL2, GL27, GL46, GL53
ESMO	1	3	0	4	GL13–GL16
American College of Gastroenterology	0	2	0	2	GL3, GL59
NCI	1	2	0	3	GL41–GL43
Royal College of Surgeons	0	1	0	1	GL48
Royal College of Radiologists	1	0	0	1	GL47
COR-CPO Piedmont	1	1	0	2	GL10, GL11
Total	33	23	3	59	GL1–GL59

R53, R75] were not available in the network of libraries we contacted and therefore they did not enter the assessment process.

The classification of the cited reviews for breast, colon and both cancers is presented in tables 3, 4 and 5.

Some guidelines did not cite any review in bibliography: for breast cancer, 2 out of 33 (6.0%) and for colorectal cancer 9 out of 23 (40%). Considering also the guidelines citing only one review, the percentages increase respectively to 24% for breast cancer and 48% for colorectal cancer.

assessment of reviews

Out of the 80 retrieved and evaluated reviews, 23 (28.7%) did not match the definition of systematic reviews, and were not evaluated with the checklist (Table 6). It was not possible to classify 17 reviews: 7 (8.7%) because the searching methods were described elsewhere, 10 (12.5%) because the searching methods were unclear. Only forty reviews (50%) were clearly systematic.

No reviews reached the A+ class score (46–50), and only five (6.2%) reached the A– class (41–45); 7 (8.7%) obtained the score of the B+ class (36–40). The figures for A– and B+ class were two (5.5%) and five (13.9%) for breast cancer and three (6.8%) and 14 (31.8%) for colorectal cancer respectively. Non-systematic, low (C class) and very low (D class) quality reviews accounted for 70% of the total, respectively for 80.6% of the breast cancer reviews and 61.4% of the colorectal cancer reviews.

Overall the 57 systematic reviews reached about 60% of the total score, with a mean score of 29.9 (C+ class). The sections most affected by low scores are: methods (average score: 6.8/15.0, only 45.6% of the standard score) and results (average score: 6.9/13.0, 53.1% of the standard). Analysing the specific chapters within the sections, the ‘quality assessment’ in the

methods section was the most affected one (average percentage of the score 26.8), but also searching and quantitative data synthesis showed low scores (respectively, 40.6% and 52.9% of the standard).

Some interesting differences among the quality classes can be pointed out. Quantitative data synthesis in the results section appear to have low scores without distinction between quality classes: also the A– class reaches only 67.5% of the standard. Title and studies characteristics appear to be affected by a low score only in C– and D classes. Discussion section presents very low scores only in the very low quality class (D class, 51.4% of the score reached), whilst abstract, searching, selection, quality assessment and quantitative data synthesis in the methods section obtained low scores in C+, C– and D classes. Quality assessment presents very low scores in all the classes except for A– and B+.

The specific scores obtained by each breast and colon cancer reviews are available on request.

quality of guidelines

The percentage of clearly systematic reviews within a guideline accounted for a variable percentage, between 0% and 100% for breast cancer, and between 0% and 86% for colon cancer (Table 3, 4 and 5).

A very low percentage of the total guidelines use systematic reviews of high quality as source of evidence. Only 10 out of 33 breast cancer guidelines (30.3%) [GL7, GL8, GL10, GL19, GL32, GL33, GL41, GL46, GL56, and GL57] and only 6 out of 23 colorectal cancer guidelines (26.1%) [GL11, GL18, GL21, GL22, GL48, and GL52] cited in bibliography at least one review of good quality (A or B quality classes).

Among the guidelines on breast cancer, 7 (21.2%) use as source of information only not systematic reviews or no review at all, whilst for colorectal cancer, this figure is 12 (52.1%).

discussion

The results of our assessment provide a sober picture of the overall quality of the sources used to write recommendations. Our score system provided 4 quality categories (A, B, C, D) which can be further divided (A+, A–, B+, B–, C+, C–, D). As described in the method section, such categories can be interpreted according to the definitions developed by the GRADE working group [6].

A sample of recommendations (and the corresponding reviews on which they were based) was identified through a wide literature search including the most relevant entities involved in the preparation of the guidelines on primary prevention and treatment of breast and colon cancer, issued since 1998 to 2003. We have made no selection, so we have evaluated a recent and reliable sample based on the main international institutions. The assessment has been performed using a QUORUM-based checklist, modified adding specific quality criteria, and adopting a choice of scores following methodological considerations. On a total of 80 reviews, non-systematic, low and very low quality reviews accounted for 70% of the total. No reviews reached the A+ class (score 46–50), and only five (6.2%) reached the A– class (41–45); seven (8.7%) obtained the score of the B+ class

Table 3. Breast cancer guidelines: classification of reviews cited in the bibliography

Ref	Total reviews	Total retrieved reviews	Systematic <i>n</i> (%) [*]	Searching strategy described elsewhere	Unclear search strategy	Not systematic	Other topics [°]	Guidelines
GL4	6	6	1 (16.7)	4	1			4
GL5	2	2	1 (50.0)	1				1
GL6	1	1				1		4
GL7	3	2	1 (50.0)			1	1	6
GL8	4	2	2 (100.0)				2	6
GL9	1	1	1 (100.0)					6
GL10	19	9	3 (33.3)	4	1	1	10	8
GL12	8	1	1 (100.0)				7	2
GL14	4	4	1 (15.0)	3				2
GL19	2	1	1 (100.0)				1	1
GL26	5	1				1	4	1
GL27	5	1		1			4	1
GL28	1	1		1				2
GL29	4	4	1 (25.0)	3				6
GL30	32	0					32	10
GL32	19	5	2 (40.0)	3			14	11
GL33	20	9	3 (33.3)	4		2	11	4
GL35	6	6	1 (100.0)	4	1			1
GL36	1	1		1				2
GL39	1	1	1 (100.0)					1
GL41	7	6	2 (33.3)	3	1		1	2
GL44	3	2		1		1	1	1
GL45	3	3		1	1	1		2
GL46	8	5	2 (40.0)	2		1	3	9
GL47	7	4		4			3	1
GL49	0	0						4
GL50	10	7	2 (28.6)	3	1	1	3	3
GL53	0	0						2
GL54	1	0					1	1
GL55	2	2				2		3
GL56	2	1	1 (100.0)				1	1
GL57	3	1	1 (100.0)				2	3
GL58	2	2	1 (50.0)			1		1

[°]Articles not focused on breast and colorectal cancer treatment and prevention (not retrieved).

^{*}Percentage out of the total retrieved reviews.

(36–40). It is worth noting that the most affected section is the methods section: on average the mean score reached is 6.8 out of 15.0, only 45.6% of the standard score.

Only 30.3% of breast cancer and 26.1% of colorectal cancer guidelines used at least one high quality review, and the percentage of guidelines using only no systematic reviews is 21.2 for breast cancer and 52.1 for colorectal cancer.

These results are not totally new, as the problem has already been raised by others before. In particular, in one study the Appraisal of Guidelines and Research and Evaluation (AGREE) Instrument was used to assess the quality of 100 guidelines (including 32 oncology guidelines) from 13 countries [2]. Curiously, this study showed that oncology guidelines had significantly higher scores on rigor of development than non-oncology guidelines (42.2% versus 29.4%; $P = 0.02$). In particular, systematic methods to search for evidence were more often used ($P = 0.01$); the methods for formulating the recommendations were more clearly described ($P = 0.02$); and health benefits, risks, and side effects were more often

considered in formulating the recommendations ($P = 0.03$). The authors concluded that the quality of practice guidelines is modest in general, but for certain domains, oncology guidelines seem to be of better quality than others. This study, as well as other similar works [5], do not take in consideration the specific aspect of the quality of the supporting evidence, which however appear to be of high relevance.

The main lessons that can be drawn from this exercise are:

- The quality of a guideline is determined by the quality of the base of evidence, and not only by the rigour of its development; some organisations producing guidelines developed specific tools for the quality assessment of the included reviews; however, none of the guidelines included in our sample detailed the results of such evaluation.
- When using recommendations oncologists should be aware that they could be based on poor underlying documents, i.e. their credibility could be undermined by lack of methodological rigour.

Table 4. Colorectal cancer guidelines: classification of reviews cited in the bibliography

Ref	Total reviews	Total retrieved reviews	Systematic <i>n</i> (%) [*]	Searching strategy described elsewhere	Unclear search strategy	Not systematic	Other topics ^o	Guidelines
GL2	0	0						1
GL3	0	0						5
GL11	15	14	8 (57.0)	1	2	3	1	12
GL13	0	0						1
GL15	0	0						
GL16	1	1			1			
GL17	4	0					4	4
GL18	3	3	2 (66.7)		1			
GL20	2	2	1 (50.0)		1			
GL21	3	3	2 (66.7)		1			
GL22	4	4	3 (75.0)		1			
GL23	0	0						
GL24	0	0						
GL25	0	0						
GL31	23	10	2 (20.0)		3	5	13	12
GL37	0	0						3
GL38	1	1				1		3
GL40	0	0						
GL42	9	5	3 (60.0)	1	1		4	3
GL43	8	6	3 (50.0)	1		2	2	3
GL48	16	10	7 (70.0)	1	1	1	6	6
GL52	33	22	19 (86.4)		1	2	11	8
GL59	4	1				1	3	2

^oArticles not focused on breast and colorectal cancer treatment and prevention (not retrieved).

*Percentage out of the total retrieved reviews.

Table 5. Guidelines on both cancers: classification of reviews cited in the bibliography

Ref	Total reviews	Total retrieved reviews	Systematic <i>n</i> (%) [*]	Searching strategy described elsewhere	Unclear search strategy	Not systematic	Other topics ^o	Guidelines
GL1	0	0						1
GL34	16	0					16	3
GL51	9	0					9	11

^oArticles not focused on breast and colorectal cancer treatment and prevention (not retrieved).

*Percentage out of the total retrieved reviews.

Table 6. Results of the QUOROM-based checklist assessment: scoring the quality of reviews on treatment and prevention of breast and colorectal cancers

Quality class	A+	A-	B+	B-	C+	C-	D	Not applicable	Total <i>n</i> (%)
Breast cancer									
Systematic	-	2	0	5	1	4	2		14 (38.9)
Unclear	-	-	-	-	4	5	-		9 (25.0)
Not systematic								13	13 (36.1)
Total <i>n</i> (%)	0 (0)	2 (5.5)	0 (0)	5 (13.9)	5 (13.9)	9 (25.0)	2 (5.6)		36 (100.0)
Colorectal cancer									
Systematic	-	3	7	7	6	1	2		26 (59.1)
Unclear	-	-	-	-	5	2	1		8 (18.2)
Not systematic								10	10 (22.7)
Total <i>n</i> (%)	0 (0)	3 (6.8)	7 (15.9)	7 (15.9)	11 (25.0)	3 (15.0)	3 (6.9)		44 (100.0)
breast + colorectal									
Total <i>n</i> (%)	0 (0)	5 (6.2)	7 (9.0)	12 (15.0)	16 (20)	12 (15.0)	5 (6.3)		80 (100.0)

- When writing recommendations, writing groups should be aware of all the methodological problems involved, and are warmly invited to consult existing manuals for the preparation of practice guidelines (e.g. [9, 12]).
- The quality of reviews, particularly when preparing new guidelines or updating old ones, should be judged by using tools such QUOROM-based tools (Table 1).

Whether the results of the current evaluation have a mainly theoretical interest or impact on oncology practice it is not clear yet, but we propend for the second choice. Although 'there is a tendency toward support for the idea that outcomes improve for patients, personnel, or organizations if clinical practice in health care is evidence-based, that is, if evidence-based clinical practice guidelines are used' [1], however, the impact of guideline quality is less documented.

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references

general references

1. Bahtsevani C, Uden G, Willman A. Outcomes of evidence-based clinical practice guidelines: a systematic review. *Int J Technol Assess Health Care* 2004; 20(4): 427–433.
2. Burgers JS, Fervers B, Haugh M et al. International assessment of the quality of clinical practice guidelines in oncology using the Appraisal of Guidelines and Research and Evaluation Instrument. *J Clin Oncol* 2004; 22(10): 2000–2007.
3. Cochrane Reviewers' Handbook. 4.2.2. The Cochrane Library, 2004, Issue 4 ([WebHelpSpecific\handbook.pdf](#)).
4. Cook DJ, Sackett DL et al. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Postdam Consultation on Meta-analysis. *J Clin Epidemiol* 1995; 48(1): 167–171.
5. Fervers B, Burgers JS, Haugh MC et al. Predictors of high quality clinical practice guidelines: examples in oncology. *Int J Qual Health Care* 2005; 17 (2): 123–132.
6. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1490–1497.
7. Mallett S, Deeks J, Altman D. Treatment of heterogeneity in systematic reviews of diagnostic tests in cancer. Abstract for 12th Cochrane Colloquium 'Bridging the Gaps'. Ottawa, Ontario, Canada. October 2–6, 2004.
8. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; 354(9193): 1896–1900.
9. New Zealand Guidelines Group. Handbook for the preparation of explicit evidence-based clinical practice guidelines. 2001. (http://www.nzgg.org.nz/download/files/nzggguideline_handbook.pdf).
10. Oxman AD, Guyatt GH, Singer J et al. Agreement among reviewers of review articles. *J Clin Epidemiol* 1991; 44(1): 91–98 (a).
11. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991; 44(11): 1271–1278 (b).
12. SIGN 50: A Guideline developer's handbook. Methodology Checklist 1: Systematic Reviews and Meta-analyses. SIGN Publication n.50, March 2004. <http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html>

list of evaluated guidelines

- GL1. Bast RC, Ravdin P, Hayes DF et al. 2000 update of Recommendations for the use of tumor markers in breast and colorectal cancer: Clinical Practice Guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19(6): 1865–1878.
- GL2. Benson AB 3rd, Desch CE, Flynn PJ et al. 2000 update of American Society of Clinical Oncology colorectal cancer surveillance guidelines. *J Clin Oncol* 2000; 18(20): 3586–3588.
- GL3. Bond JH. Polyp Guideline: diagnosis, treatment and surveillance for patients with colorectal polyps. *Am J Gastroenterol* 2000; 95: 3053–3063.
- GL4. Breast Cancer Disease Site Group. Adjuvant systemic therapy for node-negative breast cancer. Practice Guidelines Report #1–8. 2003.
- GL5. Breast Cancer Disease Site Group. Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery. Practice Guidelines Report #1–2. 2003.
- GL6. Breast Cancer Disease Site Group. Management of ductal carcinoma *in situ* of the breast. Practice Guidelines Report #1–10. 2002.
- GL7. Breast Cancer Disease Site Group. The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Practice Guidelines Report #1–5. 2003.
- GL8. Breast Cancer Disease Site Group. Surgical management of early-stage invasive breast cancer. Practice Guidelines Report #1–1. 2003.
- GL9. Cantin J, Scarth H, Levine M, Hugi M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 13. Sentinel lymph node biopsy. *Canada Medical Association Journal* 2001; 165(2): 166–173.
- GL10. Commissione Oncologia Regionale – Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte. Tumore della Mammella. Linee Guida Organizzative per la Regione Piemonte. 2002.
- GL11. Commissione Oncologia Regionale – Centro di Riferimento per l'Epidemiologia e la Prevenzione Oncologica in Piemonte. Tumori del colon-retto. Linee Guida Organizzative per la Regione Piemonte. 2001.
- GL12. Emery C, Gallagher R, Hugi M, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 10. The management of chronic pain in patients with breast cancer (2001 update). Practice Guidelines Initiative – A Cancer Care Ontario Program. 2001.
- GL13. ESMO Guidelines Task Force. Minimum clinical recommendations for diagnosis, adjuvant treatment and follow-up of colon cancer. 2002.
- GL14. ESMO Guidelines Task Force. Minimum clinical recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer. 2002.
- GL15. ESMO Guidelines Task Force. Minimum clinical recommendations for diagnosis, treatment and follow-up of advanced colorectal cancer. 2002.
- GL16. ESMO Guidelines Task Force. Minimum clinical recommendations for diagnosis, treatment and follow-up of rectal cancer. 2002.
- GL17. Figueredo A, Rumble RB, Maroun J et al. Follow-up of patients with curatively resected colorectal cancer. Practice Guidelines Report #2–9. 2003.
- GL18. Figueredo A, Zuraw L, Wong RKS et al. The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer. Practice Guidelines Report #2–13. 2003.
- GL19. Findlay BP, Walker-Dilks C, Pritchard K, and members of the Breast Cancer Disease Site Group and the Systemic Treatment Disease Site Group. Epirubicin, as a single agent or in combination for metastatic breast cancer. Practice Guidelines Report #1–6. 2002.
- GL20. Gastrointestinal Cancer Disease Site Group. Adjuvant therapy for stage II colon cancer following complete resection. Practice Guidelines Report #2–1. 2000.
- GL21. Gastrointestinal Cancer Disease Site Group. Adjuvant therapy for stage III colon cancer following complete resection. Practice Guidelines Report #2–2. 2000.
- GL22. Gastrointestinal Cancer Disease Site Group. Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer. Practice Guidelines Report #2–3. 1998.
- GL23. Gastrointestinal Cancer Disease Site Group. Use of irinotecan (Camptosar, CPT-11) combined with 5-fluorouracil and leucovorin (5FU/LV) as first-line

- therapy for metastatic colorectal cancer. Practice Guidelines Report #2–16b. 2003.
- GL24. Gastrointestinal Cancer Disease Site Group. Use of irinotecan in the treatment of metastatic colorectal cancer. Practice Guidelines Report #2–16. 2000.
- GL25. Gastrointestinal Cancer Disease Site Group. Use of raltitrexed (tomudex) in the management of metastatic colorectal cancer. Practice Guidelines Report #2–17. 2002.
- GL26. Harris S, Hugi MR, Olivetto IA, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. Canada Medical Association Journal 2001; 164(2): 191–199.
- GL27. Hillner BE, Ingle JN, Berenson JR et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel. J Clin Oncol 2000; 18: 1378–1391.
- GL28. Levine M, Moutquin JM, Walton R, Feightner. Chemoprevention of breast cancer. A joint guideline from the Canadian Task Force on Preventive Health Care and the Canadian Breast Cancer Initiative's Steering Committee on Clinical Practice Guidelines for the Care and the Treatment of Breast Cancer. Canada Medical Association Journal 2001; 164(12): 1681–1690.
- GL29. Levine M, Sawka C, Bowman DM, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 8. Adjuvant systemic therapy for women with node-positive breast cancer (2001 update). Practice Guidelines Initiative – A Cancer Care Ontario Program. 2001.
- GL30. National Breast Cancer Centre. Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer. Canberra, Commonwealth of Australia. 1999.
- GL31. National Health and Medical Research Council. Clinical practice guidelines: the prevention, early detection and management of colorectal cancer. Canberra, Commonwealth of Australia. 1999.
- GL32. National Health and Medical Research Council Breast Cancer Centre. Clinical practice guidelines for the management of advanced breast cancer. 2001.
- GL33. National Health and Medical Research Council Breast Cancer Centre. Clinical practice guidelines for the management of early breast cancer: second edition. 1999.
- GL34. National Health and Medical Research Council Breast Cancer Centre. Clinical practice guidelines for the psychosocial care of adults with cancer. 2003.
- GL35. NCCN – National Comprehensive Cancer Network. Practice Guidelines in Oncology: Breast Cancer. 2003.
- GL36. NCCN – National Comprehensive Cancer Network. Practice Guidelines in Oncology: Breast Cancer Risk Reduction. 2003.
- GL37. NCCN – National Comprehensive Cancer Network. Practice Guidelines in Oncology: Colon Cancer. 2003.
- GL38. NCCN – National Comprehensive Cancer Network. Practice Guidelines in Oncology: Colorectal Screening. 2003.
- GL39. NCCN – National Comprehensive Cancer Network. Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. 2003.
- GL40. NCCN – National Comprehensive Cancer Network. Practice Guidelines in Oncology: Rectal Cancer. 2003.
- GL41. NCI – National Cancer Institute. Breast Cancer – (PDQ) – Treatment – Health Professionals. Guidelines. 2003.
- GL42. NCI – National Cancer Institute. Colon Cancer – (PDQ) – Treatment – Health Professionals. Guidelines. 2003.
- GL43. NCI – National Cancer Institute. Rectal Cancer – (PDQ) – Treatment – Health Professionals. Guidelines. 2003.
- GL44. Olivetto IA, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 5. Management of ductal carcinoma *in situ* (DCIS) (2001 update). Practice Guidelines Initiative – A Cancer Care Ontario Program. 2001.
- GL45. Pritchard KI, Khan H, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer. Canada Medical Association Journal 2002; 166(8): 1017–1022.
- GL46. Recht A, Edge SB, Solin LJ et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19: 1539–1569.
- GL47. Royal College of Radiologists' Clinical Oncology Information Network. Guidelines on the non-surgical management of breast cancer. Clin Oncol 1999; 11: S89–S131.
- GL48. Royal College of Surgeons and Associates of Coloproctology of Great Britain and Ireland. Guidelines for the management of Colorectal Cancer. Royal College of Surgeons of England 2001.
- GL49. Scarth H, Cantin J, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 3. Mastectomy or lumpectomy? The choice of operation for clinical stages I and II breast cancer (2002 update). Practice Guidelines Initiative – A Cancer Care Ontario Program. 2001.
- GL50. SIGN – Scottish Intercollegiate Guidelines Network. Breast cancer in women. A National Clinical Guideline. Edinburgh – SIGN Publication No. 29. 1998.
- GL51. SIGN – Scottish Intercollegiate Guidelines Network. Control of pain in patient with cancer. 2000.
- GL52. SIGN – Scottish Intercollegiate Guidelines Network in collaboration with the Scottish Cancer Therapy Network. Management of colorectal cancer. A National Clinical Guideline. 2003.
- GL53. Smith TJ, Davidson NE, Schapira DV et al. American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines. J Clin Oncol 1999; 17(3): 1080–1082.
- GL54. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 9. Follow-up after treatment for breast cancer. Canada Medical Association Journal 1998; 158 (Suppl 3): S65–S70.
- GL55. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. Axillary dissection. Canada Medical Association Journal 1998; 158 (suppl 3): S22–S26.
- GL56. Verma S, Trudeau M, Pritchard K, Oliver T, and members of the Breast Cancer Disease Site Group. The role of taxanes in the management of metastatic breast cancer. Practice Guidelines Report #1–3. 2003.
- GL57. Warr D, Johnston M, and members of the Breast Cancer Disease Site Group. Use of bisphosphonates in women with breast cancer. Practice Guidelines Report #1–11. 2002.
- GL58. Whelan T, Olivetto I, Levine M, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 6. Breast radiotherapy after breast-conserving surgery (2003 update). Practice Guidelines Initiative – A Cancer Care Ontario Program. 2002.
- GL59. Winawer SJ, Fletcher RH, Miller L et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 2003; 124: 544–560.

list of reviews mentioned in the evaluated guidelines

- R1. Advanced Colorectal Cancer Meta-Analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. J Clin Oncol 1994; 12(5): 960–969.
- R2. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992; 10(6): 896–903.
- R3. Bellacosa A, Genuardi M, Anti M. Hereditary nonpolyposis colorectal cancer: review of clinical, molecular genetics, and counselling aspects. Am J Med Genet 1996; 62: 353–364.
- R4. Best L, Simmonds P, Baughan C et al. Palliative chemotherapy for advanced or metastatic colorectal cancer (Cochrane Review). In: The Cochrane Library 2000; Issue 4: Oxford: Update Software.
- R5. Bosset JF, Horiot JC. Adjuvant treatment in the curative management of rectal cancer: a critical review of the results of clinical randomized trials. Eur J Cancer 1993; 29A: 770–774.

- R6. Bradley SJ, Weaver DW, Bouwman DL. Alternatives in the surgical management of *in situ* breast cancer. A meta-analysis of outcome. *Am Surg* 1990; 56: 428–432.
- R7. Brewer DA, Fung CL, Chapuis PH, Bokey EL. Should relatives of patients with colorectal cancer be screened? A critical review of the literature. *Dis Colon Rectum* 1994; 37: 1328–1338.
- R8. Budzar AU, Jonta W, Howell A et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in of postmenopausal women with advanced breast cancer: result of overview analysis of two phase III trials. *J Clin Oncol* 1996; 14: 2000–2011.
- R9. Camma C, Giunta M, Fiorica F et al. Preoperative radiotherapy for resectable rectal cancer. A meta-analysis. *JAMA* 2000; 284: 1008–1015.
- R10. Carter S, Winslet M. Delay in the presentation of colorectal carcinoma: a review of causation. *Int J Colorectal Dis* 1998; 13: 27–31.
- R11. Cole BF, Gelber RD, Gelber S, Coates AS GA. Polychemotherapy for early breast cancer. An overview of the randomized trials with quality-adjusted survival analysis. *Lancet* 2001; 358: 277–286.
- R12. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997; 350: 1047–1059.
- R13. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; 358: 1291–1304.
- R14. Corrao G, Bagnardi V, Zamboni A, Arico S. Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction* 1999; 94: 1551–1573.
- R15. Crandall CJ. Estrogen replacement therapy and colon cancer: a clinical review. *J Women Health Gen Based Med* 1999; 1155–1166.
- R16. De Gramont A, Louvet C, Andre T et al. Groupe d'Etude et de Recherche sur le Cancer de l'Ovaire et Digestif (GERCOD). A review of GERCOD trials of bimonthly leucovorin plus 5-FU 48-h continuous infusion in advanced colorectal cancer: evolution of a regimen. *Eur J Cancer* 1998; 34: 619–626.
- R17. Dubé S, Heyen P, Jenicek M. Adjuvant chemotherapy in colorectal carcinoma. Results of a meta-analysis. *Dis Colon Rectum* 1997; 40: 35–41.
- R18. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; 48: 526–535.
- R19. Early Breast Cancer Trialists' Collaborative Group. Effect of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. *N Engl J Med* 1988; 319: 1681–1692.
- R20. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 1995; 333: 1444–1455.
- R21. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer. An overview of the randomized trials. *Lancet* 2000; 355: 1757–1770.
- R22. Early Breast Cancer Trialists' Collaborative Group. Multi-agent chemotherapy for early breast cancer (Cochrane Review). In: *The Cochrane Library* 2002; (Issue 1): Oxford: Update Software.
- R23. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer (Cochrane Review). In: *The Cochrane Library* 2002; (Issue 1): Oxford: Update Software.
- R24. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer. An overview of the randomized trials. *Lancet* 1998; 352: 930–942.
- R25. Early Breast Cancer Trialists' Collaborative Group. Radiotherapy for early breast cancer (Cochrane Review). In: *The Cochrane Library* 2002; (Issue 2): Oxford: Update Software.
- R26. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992; 339: 1–15: 71–85.
- R27. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer (Cochrane Review). In: *The Cochrane Library* 2002; (Issue 1): Oxford: Update Software.
- R28. Fossati R, Confalonieri C, Torri V et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol* 1998; 16: 3439–3460.
- R29. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 725–731.
- R30. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999; 106: 574–582.
- R31. Harmantas A, Rotstein LE, Langer B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. *Cancer* 1996; 78: 1639–1645.
- R32. Hebert-Croteau N. A meta-analysis of hormone replacement therapy and colon cancer in women. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 653–659.
- R33. Houlston RS, McCarter E, Parbhoo S, Scurr JH, Slack J. Family history and risk of breast cancer. *J Med Genet* 1992; 29: 154–157.
- R34. Howe GR, Aronson KJ, Benito E et al. The relationship between intake of dietary fat and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control* 1997; 8: 215–218.
- R35. Howe GR, Benito E, Castekatti R et al. Dietary intake of fibre and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 1992; 84: 1887–1896.
- R36. Jacobson JS, Workman SB, Kronenberg F. Research on complementary/alternative medicine for patients with breast cancer: a review of the biomedical literature. *J Clin Oncol* 2000; 18(3): 668–683.
- R37. Jonker DJ, Maroun JA, Kocha W. Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. *Br J Cancer* 2000; 82: 1789–1794.
- R38. Kelsey JL. A review of the epidemiology of breast cancer. *Epidemiol Rev* 1979; 1: 74–109.
- R39. Kelsey JL, Whittemore AS. Epidemiology and primary prevention of cancers of the breast, endometrium and ovary. A brief overview. *Ann Epidemiol* 1994; 4: 89–95.
- R40. Kim YI. AGA technical review: impact of dietary fiber on colon cancer occurrence. *Gastroenterol* 2000; 118: 1235–1257.
- R41. Klijn JG, Blamey RW, Boccardo F et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; 19(2): 343–353.
- R42. Liver Infusion Meta-analysis Group. Portal vein chemotherapy for colorectal cancer: a meta-analysis of 4000 patients in 10 studies. *J Natl Cancer Inst* 1997; 89: 497–505.
- R43. Lonning PE. Treatment of early breast cancer with conservation of the breast. A review. *Acta Oncol* 1991; 30(7): 779–792.
- R44. Lustosa SAS, Matos D. Stapled versus handsewn methods for colorectal anastomosis surgery (Cochrane Review). In: *The Cochrane Library* 2001; Issue 3: Oxford: Update Software.
- R45. Lynch HT, Smyrk T. Hereditary nonpolyposis colorectal cancer (Lynch syndrome): an updated review. *Cancer* 1996; 78: 1149–1167.
- R46. Lynch HT, Smyrk TC, Watson P et al. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. *Gastroenterology* 1993; 104: 1535–1549.
- R47. MacRae HM, McLeod RS. Handsewn versus stapled anastomoses in colon and rectal surgery: a meta-analysis. *Dis Colon Rectum* 1998; 41: 180–189.
- R48. Messori A, Cattel F, Trippoli S, Vaiani M. Survival in patients with metastatic breast cancer: analysis of randomized studies comparing oral aromatase inhibitors versus megestrol. *Anticancer Drugs* 2000; 11: 701–706.
- R49. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; 16(1): 301–308.

- R50. Meta-analysis Group in Cancer. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. *J Natl Cancer Inst* 1996; 88(5): 252–258.
- R51. Meta-analysis Group in Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol* 1998; 16(11): 3537–3541.
- R52. Morris AD, Morris RD, Wilson JF et al. Breast-conserving therapy versus mastectomy in early-stage breast cancer: a meta-analysis of 10 survival. *Cancer J Sci Am* 1997; 3: 6–12.
- R53. Munro AJ, Bentley AHM. Adjuvant radiotherapy in operable rectal cancer: a systematic review. *Semin Colon Rectal Surg* 2002; 13: 31–42.
- R54. Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. *Obstet Gynecol* 1999; 93: 880–888.
- R55. Ng AK, Recht A, Busse PM. Sphincter preservation therapy for distal rectal carcinoma: a review. *Cancer* 1997; 79(4): 671–683.
- R56. NHS Centre for Reviews and dissemination. The management of primary breast cancer. *Effect Health Care* 1996; 2: 1–16.
- R57. Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* 2002; 98: 241–256.
- R58. Ooi BS, Tjandra JJ, Green MD. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Dis Colon Rectum* 1999; 42(3): 403–418.
- R59. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival – a Bayesian meta-analysis. *Ann Surg Oncol* 1999; 6: 109–116.
- R60. Pavlakis N, Stockler M. Biphosphonates in breast cancer (Cochrane Review). In: *The Cochrane Library* 2002; (Issue 1): Oxford: Update Software.
- R61. Petrek JA, Blackwood MM. Axillary dissection: current practice and technique (review). *Curr Probl Surg* 1995; 32: 257–323.
- R62. Pharoah PD, Day NE, Duffy S et al. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997; 71: 800–809.
- R63. Potter JD. Nutrition and colorectal cancer. *Cancer Causes Control* 1996; 8: 127–146.
- R64. Potter JD, Slattey ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. *Epidemiol Rev* 1993; 15: 499–545.
- R65. Recht A, Houlihan MJ. Axillary lymph nodes and breast cancer: a review. *Cancer* 1995; 76: 1491–1512.
- R66. Rhodes M, Bradburn DM. Overview of screening and management of familial adenomatous polyposis. *Gut* 1992; 33: 125–131.
- R67. Ruffin WK, Stacey-Clear A, Younger J, Hoover HC. Jr. Rationale for routine axillary dissection in carcinoma of the breast (review). *J Am Coll Surg* 1995; 180: 245–251.
- R68. Sakamoto J, Hamada C, Kodaira S, Nakazato H, Ohashi Y. Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomized trials. *Jpn J Clin Oncol* 1999; 29: 78–86.
- R69. Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev* 2001; 10: 439–446.
- R70. Saunders CM, Baum M. Breast cancer and pregnancy: a review. *J Roy Soc Med* 1993; 86: 162–165.
- R71. Simmonds PC for the Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. *BMJ* 2000; 321: 531–535.
- R72. Simpson T, Thirlby RC, Dail DH. Surgical treatment of ductal carcinoma *in situ* of the breast: 10 to 20 year follow-up (review). *Arch Surg* 1992; 127: 468–472.
- R73. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. *Br J Surg* 1998; 85(9): 1233–1241.
- R74. Spillane AJ, Sacks NP. Role of axillary surgery in early breast cancer: review of the current evidence. *Aust N Z J Surg* 2000; 70: 515–524.
- R75. Stockler M, Wilcken N, Ghersi D, Simes RJ. The management of advanced breast cancer: systemic reviews of randomized controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy. Woolloomooloo, NHMRC National Breast Cancer Centre. 1997.
- R76. Stockler M, Wilcken N, Ghersi D, Simes RJ. Systematic reviews of systemic therapy for advanced breast cancer. *Cancer Treat Rev* 2000; 26: 168.
- R77. Sugarbaker PH, Corless S. Influence of surgical techniques on survival in patients with colorectal cancer: a review. *Dis Colon Rectum* 1982; 25: 545–557.
- R78. Thirion P, Wolmark N, Haddad E et al. Survival impact of chemotherapy in patients with colorectal metastases confined to the liver: a re-analysis of 1,458 non-operable patients randomized in 22 trials and 4 meta-analyses. *Proc Am Soc Clin Oncol* 1999; 10(11): 1317–1320.
- R79. Thomas PR, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. *Radiother Oncol* 1988; 13(4): 245–252.
- R80. Vezeridis MP, Bland KI. Review: management of ductal carcinoma *in situ*. *Surg Oncol* 1994; 3: 309–325.
- R81. Whelan TJ, Julian J, Wright J et al. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000; 18: 1220–1229.
- R82. Wille-Jorgensen P, Rasmussen MS. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery (Cochrane Review). In: *The Cochrane Library* 2001; (Issue 3): Oxford: Update Software.
- R83. Wong R, Thomas G, Cummings B et al. In search of a dose-response relationship with radiotherapy in the management of recurrent rectal carcinoma in the pelvis: a systematic review. *Int J Radiat Oncol Biol Phys* 1998; 40(2): 437–446.