

Clinical Utility of Cancer Family History Collection in Primary Care

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Preface

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

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

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

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

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Structured Abstract

Objectives: This systematic review aimed to evaluate, within unselected populations: the (1) performance of family history (FHx)-based models in predicting cancer risk; (2) overall benefits and harms associated with established cancer prevention interventions; (3) impact of FHx-based risk information on the uptake of preventive interventions; and (4) potential for harms associated with collecting cancer FHx.

Data Sources: MEDLINE[®], EMBASE[®], CINAHL[®] Cochrane Central[®], Cochrane Database of Systematic Reviews, and PsycINFO were searched from 1990 to June 2008 inclusive. Cancer guidelines and recommendations were searched from 2002 forward and systematic reviews from 2003 to June 2008.

Review Methods: Standard systematic review methodology was employed. Eligibility criteria included English studies evaluating breast, colorectal, ovarian, or prostate cancers. Study designs were restricted to systematic review, experimental and diagnostic types. Populations were limited to those unselected for cancer risk. Interventions were limited to collection of cancer FHx; primary and/or secondary prevention interventions for breast, colorectal, ovarian, and prostate cancers.

Results: *Accuracy of models.* Seven eligible studies evaluated systems based on the Gail model, and on the Harvard Cancer Risk Index. No evaluations demonstrated more than modest discriminatory accuracy at an individual level. No evaluations were identified relevant to ovarian or prostate cancer risk.

Efficacy of preventive interventions. From 29 eligible systematic reviews, seven found no experimental studies evaluating interventions of interest. Of the remaining 22, none addressed ovarian cancer prevention. The reviews were generally based on limited numbers of randomized or controlled clinical trials. There was no evidence either to support or refute the use of selected chemoprevention interventions, there was some evidence of effectiveness for mammography and fecal occult blood testing.

Uptake of intervention. Three studies evaluated the impact of FHx-based risk information on uptake of clinical preventive interventions for breast cancer. The evidence is insufficient to draw conclusions on the effect of FHx-based risk information on change in preventive behavior.

Potential harms of FHx taking. One uncontrolled trial evaluated the impact of FHx-based breast cancer risk information on psychological outcomes and found no evidence of significant harm.

Conclusions: Our review indicates a very limited evidence base with which to address all four of the research questions: 1) the few evaluations of cancer risk prediction models do not suggest useful individual predictive accuracy; 2) the experimental evidence base for primary and secondary cancer prevention is very limited; 3) there is insufficient evidence to assess the effect of FHx-based risk assessment on preventive behaviors; and 4) there is insufficient evidence to assess whether FHx-based personalized risk assessment directly causes adverse outcomes.

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Appendixes and Evidence Tables for this report are provided electronically at <http://www.ahrq.gov/downloads/pub/evidence/pdf/famhistory/famhist2.pdf>.

Executive Summary

Family history reflects the combined influences of genetics, environmental exposures, and behaviors within families,¹ and is a risk factor for some clinically important chronic diseases such as cardiovascular disease, diabetes mellitus, stroke, and several cancers.^{2,3} Family history reflects genomic, social and environmental risk which is shared between relatives. This ‘compressed information’⁴ may provide predictive information independent of other known risk factors.

Individual risk stratification systems based on family history may carry valuable predictive information for individual patients, but they need to be validated for application in routine practice. The usefulness of family history-based risk stratification systems in disease prevention depends on (a) accurate reporting and capture of family history information, (b) valid methods of risk classification, (c) effective preventive interventions to manage disease risk, and (d) evidence that the use of family history information provides incremental net benefit over and above non-family history-based alternative approaches. With the exception of accuracy of reporting, this systematic review is designed to inform all of these issues.

Scope and Purpose of the Systematic Review

This report, which builds on a previous evidence report⁵ on the topic of tools for collecting and interpreting family history information, addresses the clinical utility of routinely using family history information in risk assessment and prevention for breast, ovarian, colorectal, and prostate cancers in primary care. The specific research questions are:

1. Which risk stratification algorithms or guidelines delineate risk accurately, and in a clinically meaningful way?
2. For which behaviors and clinical preventive services (‘interventions’) is there evidence of benefits in terms of actual reduction in disease risk, and what harms, if any, have been identified?
3. For those interventions identified as being based on reasonable evidence, what is the evidence that providing information on risk status results in behavior change or increased uptake of services on the part of individual patients?
4. What are the harms or risks to individual patients that may result from the collection of family history information in itself, and/or the provision of family history-based risk information?

These questions represent the links in the chain between taking family history and producing benefit: Does family history predict future risk of cancer? If so, are there interventions to reduce this risk, and do they also carry their own risks? Does a family history-based approach lead to higher uptake of preventive interventions? Are there any direct harms which arise from a family history-based approach?

This review’s focus is therefore firmly on the application of family history taking from general populations under the care of primary care providers such as family physicians, internists, nurse practitioners, and obstetricians. We sought to examine the capture and use of

family history information as an activity practiced in primary care, where patients are not pre-selected for risk, and where the approach to capturing information is heavily influenced (often constrained) by contextual factors,⁶ and where the preventive interventions available are those that can be recommended by a primary care practitioner. This is distinctly different from clinical genetics assessment, where the central focus is on extensive family history capture, validation, and assessment, where the patient population is usually pre-selected for high risk status.

Methods

Standard systematic review methodology was employed. MEDLINE[®], EMBASE[®], CINAHL[®], Cochrane Central[®], Cochrane Database of Systematic Reviews, and PsycINFO were searched from 1990 to June 2008 inclusive. Cancer guidelines and recommendations were searched from 2002 forward and systematic reviews from 2003 to June 2008.

Eligibility criteria included English studies evaluating breast, colorectal, ovarian, or prostate cancers. Study designs varied by question, but were restricted to systematic reviews of effectiveness (Question 2), and experimental (Questions 3 and 4) and diagnostic evaluation (Question 1) types. Populations were limited to those unselected for cancer risk. Interventions were the structured/systematic collection of family history (Questions 1, 3, and 4) and primary or secondary cancer prevention (screening) interventions (Question 2). The outcomes were disease incidence or proxy (Questions 1 and 2), uptake of recommended preventive interventions (Question 3), and harms (e.g., psychological distress) (Question 4).

Results

Our comprehensive search yielded 10,644 unique citations; from these 9,765 were excluded as they were not an English language publication, not on the cancers of interest, or on topic for any of the four research questions. The remaining 879 citations were screened at full text and from these a total of 12 primary studies and 29 systematic reviews were eligible.

Research Q1: Which Risk Stratification Algorithms or Guidelines, Delineate Risk Accurately and in a Clinically Meaningful Way?

General approach. The purpose of this question was to establish whether family history-based risk stratification systems (of any kind) could accurately predict risk in individual patients. We reviewed published studies that examined the discriminatory accuracy of models (algorithms, guidelines) that used family history information to predict individual risk of breast, ovarian, colorectal or prostate cancer. To be eligible, a model had to incorporate specified family history information (either alone or with other personal or clinical information which would be routinely available on all patients to a primary care practitioner), and validation data in a defined general population had to be presented. The main outcome of interest was discriminatory accuracy, which reflects the proportion of individuals correctly classified by the tool with respect to actual disease incidence. This was variously presented as a concordance statistic, the area under the curve in receiver operating characteristic (ROC) analyses, or correlation coefficient, and reflects the usefulness of the model for use in the assessment of individual patients.

Findings. Eight evaluation studies were identified as eligible after full text review.⁷⁻¹⁴ All tools except one were designed for breast cancer risk assessment. The breast cancer tools were all generally related to the original Gail model,¹⁵ including the model developed from the Contraceptive and Reproductive Experiences Study (the CARE model⁷). The Harvard Cancer Risk Index¹⁶ (HCRI) was developed for application to a number of cancers, but an eligible validation study was identified only for colon cancer. No eligible studies were identified of tools based strictly on family history information alone.

The original evaluation of the Gail model was conducted in a predominantly white U.S. female population,⁸ and reported discriminatory accuracy in terms of a Pearson correlation coefficient (0.67). The other breast cancer models were evaluated in white,⁹ “diverse”,¹³ African American,^{7,10} and Italian^{11,12} populations. These studies reported concordance statistics in the range of 0.55-0.59, indicating very modest discriminatory accuracy.

The HCRI was evaluated for prediction of colon cancer¹⁴ in secondary analyses of cohort data, and reported concordance statistics of 0.67 and 0.71 for women and men, respectively. This suggests moderate discriminatory accuracy (67 and 71 percent correct prediction of eventual cancer status respectively, 50 percent being that expected by chance alone).

Research Q2: For Which Behaviors and Clinical Preventive Services is There Evidence of Benefit in Terms of Actual Reduction in Disease Risk, and What Harms, if any, Have Been Identified?

General approach. The purpose of this question was to establish the link between stratifying cancer risk and being able to intervene to alter that risk, and not to conduct an exhaustive review of the extensive literature around cancer risk factors. We therefore evaluated published systematic reviews on a range of interventions which are generally recommended as part of cancer risk reduction strategies in primary care settings. Where multiple reviews addressing the same intervention were identified, we selected the most recent or most comprehensive for reporting, and considered differences in methodological quality.¹⁷

Findings. Twenty-nine systematic reviews were retained after full text review, addressing four chemoprevention interventions (antioxidant supplementation, calcium supplementation, non-steroidal anti-inflammatory drugs (NSAIDs), but not COX-2 inhibitors and statins) and five screening interventions (breast self-examination (BSE), screening mammography, fecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), and prostate specific antigen (PSA) for three cancers (breast, colorectal, prostate). No reviews were identified for several interventions of interest, and none were relevant to ovarian cancer prevention.

Data were extracted from the 10 reviews that represented the most comprehensive, up-to-date, and high quality evidence.¹⁸⁻²⁷ Of the remainder where data were not abstracted, 12 reported overlapping data,²⁸⁻³⁹ five did not identify primary intervention studies despite these being designed to do so,⁴⁰⁻⁴⁴ and two did not report usable data.^{45,46}

Overall quality assessment suggested low risk for bias, the main area of weakness being failure to describe adequate control of bias in study selection.^{18-20,22,23,27} Other issues were incomplete description of search methods,^{23,27} failure to describe criteria for assessing the validity of primary studies,^{20,25,26} and failure to cite the validity assessments of included studies.^{20,26}

Breast Cancer

Five systematic reviews synthesized evidence on chemoprevention (antioxidants and statins) and screening (breast self-examination (BSE) and screening mammography).

Antioxidants. One review¹⁸ evaluated supplements that contained any combination of β -carotene, vitamin C, vitamin E, selenium, zinc, and other antioxidants, and concluded no evidence of a protective effect of any combination against breast cancer (RR 1.00, 95 percent CI 0.90-1.09) at one year followup. A second review¹⁹ examined vitamin E alone or in any combination in three high quality randomized controlled trials (RCT) and concluded no evidence of a reduction in breast cancer incidence (RR 0.99, 95 percent CI 0.90-1.10).

Statins. One review,²⁰ suggested that statins appeared to confer neither a protective nor a harmful effect on breast cancer incidence (RR 1.01, 95 percent CI 0.79-1.30).

BSE. One review²¹ showed no impact of BSE on breast cancer mortality (RR 1.05, 95 percent 0.98-1.14).

Screening mammography. The most recent comprehensive review,²² suggested that screening mammography was associated with reduced breast cancer mortality at 13 years (RR 0.80, 95 CI 0.73-0.88), although concerns were raised about inadequate bias control in some primary trials. No effect on overall mortality was noted (RR 1.00, 95 percent CI 0.96-1.04).

Colorectal Cancer

Six reviews evaluated interventions in colorectal cancer (CRC) prevention, four on chemoprevention (antioxidants, NSAIDs, statins) and two on screening (fecal occult blood testing (FOBT) and flexible sigmoidoscopy (FS)).

Antioxidants. One review¹⁸ evaluated supplements which contained any combination of β -carotene, vitamin C, vitamin E, selenium, zinc, and showed no evidence of a protective effect against CRC incidence (RR 1.00, 95 percent CI 0.90-1.10). A second review¹⁹ evaluated vitamin E given in any combination and found no evidence of an effect on CRC incidence (RR 0.95, 95 percent CI 0.81-1.12).

NSAIDs. One review evaluated low dose ASA,²³ and found no evidence of an effect on CRC incidence (RR 1.02, 95 percent CI 0.84-1.25), CRC mortality (RR not reported) or adenoma incidence (RR 0.85, 95 percent CI 0.68-1.1) at 5 years.

Statins. One review²⁰ showed neither a protective nor harmful effect of statins on CRC incidence (pooled RR 1.02, 95 percent CI 0.89-1.16) or CRC mortality (RR 0.33, 95 percent CI 0.07-1.63).

FOBT. One review²⁴ examined FOBT (guaiac or immunochemical) in studies of at least two rounds of screening were compared with no screening. A statistically significant effect of screening on CRC mortality was observed (RR 0.84, 95 percent CI 0.78-0.90), and no effect on all-cause mortality (RR 1.00, 95 percent CI 0.99-1.01).

FS. A single review²⁵ examined the evidence for FS in CRC screening, identifying a single RCT comparing FS plus FOBT against FOBT alone. No statistically significant effect was found on CRC mortality or incidence (RR 0.78, 95 percent CI 0.36-1.73 and 1.37, 95 percent CI 0.88-2.15, respectively).

Prostate Cancer

Five reviews synthesized evidence in relation to prostate cancer prevention: four relating to chemoprevention (antioxidants, calcium, and statins) and one relating to screening (prostate-specific antigen (PSA) with digital rectal examination (DRE) and trans-urethral ultrasound (TRUS) biopsy).

Antioxidants. One review¹⁸ evaluated supplements that contained any combination of β -carotene, vitamin C, vitamin E, selenium, zinc, and other antioxidants. The pooled analysis of all antioxidants showed no effect on prostate cancer incidence (RR 0.87, 95 percent CI 0.74-1.02), and a reduced risk associated with vitamin E specifically (RR 0.82, 95 percent CI 0.67-0.99). A second review¹⁹ of vitamin E in any combination showed a negative association with prostate cancer incidence (RR 0.85, 95 percent CI 0.74, 0.96).

Calcium. One review evaluated calcium supplementation and prostate cancer risk,²⁶ where this was a secondary outcome in a single colorectal adenoma prevention trial.⁴⁷ It suggested a statistically significantly lower incidence of prostate cancer in the supplement group until 2 years after supplementation was discontinued (rate ratio 0.52, 95 percent CI 0.28-0.98), at which point the risk in both groups converged.

Statins. One review²⁰ examined the effectiveness of statins on prostate cancer. The results indicated that statins appeared to neither increase nor decrease the risk of prostate cancer incidence or mortality (RR 1.00, 95 percent CI 0.85-1.17 and RR 0.99, 95 percent CI 0.14-7.01, respectively).

PSA-based screening. One review²⁷ examined the effectiveness of PSA-based population screening (with DRE and TRUS biopsy) in two trials, one with an annual and the other a three times yearly, screening cycle. No statistically significant impact of screening on prostate cancer mortality was found (RR 1.01, 95 percent CI 0.80-1.29).

Research Q3: For Those Interventions Identified as Being Based on Reasonable Evidence, What is the Evidence That Providing Information on Risk Status, Results in Behavior Change or Increased Uptake of Services on the Part of Individual Patients?

General approach. The focus of this question was behavior: whether giving people personalized risk advice based on their family history would lead to a higher adherence with preventive recommendations. We evaluated intervention studies in which the outcomes were actual risk-reduction behavior, focusing on interventions that were considered standard of care when the primary study was conducted.

Findings. Three studies⁴⁸⁻⁵⁰ were eligible, all focusing on uptake of screening interventions for breast cancer as the target behavior. Two were randomized controlled trials^{49,50} and examined different levels of personalization of risk information. The third⁴⁸ was an uncontrolled before-after study.

One trial⁴⁸ showed a borderline statistically significant difference ($P = 0.05$) in mammography uptake (about 8 percent) between intervention and control groups. The other two studies were null. The community pharmacy study⁴⁶ was the only one to examine other behaviors, and showed a statistically significant increase in self-reported BSE, but not CBE.

Research Q4: What are the Harms or Risks to Individual Patients That may Result From the Collection of Family History Information in Itself, and/or the Provision of Family History-Based Risk Information?

General approach. The purpose of this question was to identify whether the process of capturing family history and feeding back personalized risk, in and of itself, was associated with identifiable harms. We reviewed published intervention studies which examined the direct impact of family history-based risk information on quality of life, psychological, and social impact, where these could be directly attributed to this intervention and not subsequent investigations or preventive activities.

Findings. One eligible study was identified,⁵¹ an uncontrolled before-after study designed to evaluate the psychological impact of providing family history information and receiving a personalized risk assessment for breast cancer. In all participants, no statistically significant change in anxiety or cancer worry between baseline and followup was observed. In participants whose risk assessment indicated “population risk”, a small reduction in self-perceived risk was observed ($P < 0.01$). In participants who required further assessment (‘true’ high risk and ‘false positive’ groups), higher baseline cancer risk perception scores were observed compared with the group assessed as population risk ($P < 0.001$ for ‘higher risk’ group and $P = 0.003$ for ‘false positive’ group).

Discussion and Conclusions

The purpose of this review was to establish the evidence base to answer the question, “In primary care settings, and in relation to breast, ovarian, colorectal or prostate cancers, would the routine use of family history-based risk assessment be likely to lead to net health benefits?” We identified a very limited evidence base for all four of the research questions.

While there are a number of FHx-based cancer risk stratification systems, no evaluations have been published of any based only on FHx information. Of those models which include FHx information along with other clinical variables, published validations suggest good epidemiological calibration but no more than modest individual discriminatory accuracy. The models evaluated were not necessarily developed for general clinical use.

The experimental evidence base, represented in published systematic reviews, for primary and secondary cancer prevention in general populations is very limited. The most consistent evidence supports screening mammography and FOBT-based colorectal screening strategies, with equivocal evidence for vitamin E and calcium in reducing the risk of prostate cancer. The review likely did not include some experimental evidence for interventions which have not been examined in systematic reviews, but which would be relevant to the main study questions.

There is insufficient evidence to assess the effect of FHx-based risk assessment on preventive behaviors. Very few trials have been conducted, and none in settings resembling routine primary care practice. There is also insufficient evidence to assess definitively whether FHx-based personalized risk assessment directly causes adverse outcomes; the results of the single study available indicate the need to take into account baseline psychological status and risk perception in assessing the impact of FHx-based risk information.

Conclusions

1. The evidence for the predictive accuracy of algorithms in primary care populations was very limited. Although many tools were identified that incorporated some family history information, no evaluations of solely family history-based tools. The tools on which it was possible to comment related mainly to breast cancer.

Recommendations for future research:

- The actual performance of tools based only on family history should be formally examined in primary prospective studies, and/or in secondary analysis of large cohort studies.
- The performance of individual family history components of different risk stratification models which use a wider range of factors (including those examined in this report) should be examined separately from the non-family history components, in order to determine whether they provide sufficient predictive power in the absence of the non-family history factors.
- For clinical relevance, the focus of validation should be discriminatory accuracy at the individual patient level.
- More definitive evaluation should examine the effect on health outcomes when risk stratification systems are used in combination with preventive interventions, in actual practice settings. This cannot be done with secondary analyses of observational data and requires well-designed intervention studies.

2. The evidence establishing the efficacy of interventions for primary and secondary prevention based on systematic reviews of randomized or controlled clinical studies in unselected populations is very limited. Interventions for which there were reviews include chemoprevention (antioxidants, calcium, NSAIDs, and statins) and screening interventions (BSE, mammography, FBOT, FS, and PSA) for breast, colorectal and prostate cancers. No reviews were found for ovarian cancer. It is likely that this review excluded effectiveness data available from RCTs of interventions which have not yet been the subject of systematic reviews.

Recommendations for future research:

- The large amount of evidence on potential primary cancer preventive interventions obtained from observational studies of cancer risk factors should continue to be further evaluated in well-designed randomized controlled trials.
- Further systematic reviews should be conducted to examine the full range of potentially preventive interventions

3. Within primary care populations, there is very limited evidence to support or refute the effect on risk-reducing behavior changes (e.g., lifestyle changes or uptake of recommended clinical interventions) of taking a family history and using it to personalize risk of breast, ovarian, colorectal or prostate cancer.

Recommendations for future research:

- Well-designed trials are required that compare family history-based, personalized risk advice with standard of care on risk reducing behaviors in populations at different risk levels (including population risk).

4. In primary care populations, there is very limited information to evaluate direct harm incurred from the routine practice of taking family history and using it to personalize risk information.

Recommendations for future research:

- Trials of family history taking as an intervention should include capture of data to examine the full range of potential impacts on individuals. Baseline data on psychological status should be captured so that this can formally be adjusted for in outcome analyses.

5. Research on the use of family history tools, risk stratification systems, and family history-based personalized prevention advice should take into account evidence on the factors likely to promote their effective use in practice, such as the educational needs of primary care practitioners and issues which act as barriers or constraints to their implementation in practice.

Evidence Report

Chapter 1. Introduction

Background

The Potential of Family History Information in Preventing Cancer

Family history has always been a core tool in medical practice. A person's family history reflects the combined influences of genetics, environmental exposures, and behaviors within families.¹ A large number of reports demonstrate that a positive family history is a risk factor for many chronic diseases of clinical importance, including cardiovascular disease, diabetes mellitus, stroke, and several cancers.^{2,3} The greater the number of relatives affected by a disorder, the younger their ages of onset, and the closer the relationship to the individual in question, the more likely it is that the family's disease experience has a genetic basis. However, given the low population prevalence of genetic forms of common, complex disorders, a screening approach based on identifying fairly extreme family histories offers very limited public health or clinical utility in practice.

Historically, the practice of clinical genetics has been largely predicated on detecting individuals marked out by membership in families with unusual patterns of disease, and who are at significantly elevated individual risk as a result of rare genetic disorders that have relatively high penetrance. The alternative approach, which is the focus of this review, is to recognize that family clustering of disease risk reflects combinations of lower penetrance, and moderate risk alleles which are reasonably common within a population. The latter example, a high prevalence of people with slightly or moderately elevated inherited disease risk, would lead to a much higher total disease burden within a population than that associated with a low prevalence of people at very high risk.⁵² Under the right circumstances, a 'genomic test' – such as the presence of particular family history characteristics - could have a significant positive predictive value.

Several years ago, Yoon and colleagues¹ illustrated this point. They demonstrated how even fairly simple family history information could be used to clarify the risk of a number of common, complex disorders. Based on published data, they suggested that a healthy 23 year old man could have the following lifetime risks of:

- 60 percent for cardiovascular disease (based on one male first degree relative (1DR) diagnosed after age 60)
- 50 percent for colorectal cancer (based on two 1DRs diagnosed before age 50); and
- 30 percent for type 2 diabetes (based on one 1DR diagnosed after age 60)

Importantly, their risk prediction was based on family history information which would not be considered extreme. This application of family history information complements the vision of 'personalized medicine' which physician-geneticist Francis Collins M.D., Ph.D., predicted would be available in 2010, in the form of DNA-based genome profiling tests.⁵³ While recent research indicates that such profiling is possible in principle,⁵⁴ it is evident that this is not yet a technology ready for routine implementation in health care.^{52,55} Until such time, family history represents a potential source of useful predictive information already available to any health care provider.

Discussing the role of family history in coronary heart disease risk, Kardia and colleagues describe the family history as “compressed information” which integrates risks arising from shared genomic components, and social and physical environments.⁴ They expand:

“For, example, we know that parents and children share exactly half their genes. This translates practically into sharing one copy of the 30,000 to 50,000 genes estimated to be in the human genome in the nucleus of each nucleated cell in the human body. ... it is quite possible that even with our ability to measure hundreds and thousands of genes and environments we may find that family history is the best, low-cost way to identify the at-risk subgroups in the population. This will be especially true if gene-gene and gene-environment interactions play a major role in determining risk of future disease.”

This perspective is supported by the work of Butterworth,³ who recently conducted a comprehensive meta-analysis of the risk conferred by family history for a number of common, complex disorders, including the cancers of interest in this review. Table 1 summarizes his findings for colorectal, breast, ovarian, and prostate cancer.

Table 1. Pooled relative risk estimates (95% confidence intervals) for cancers of interest³

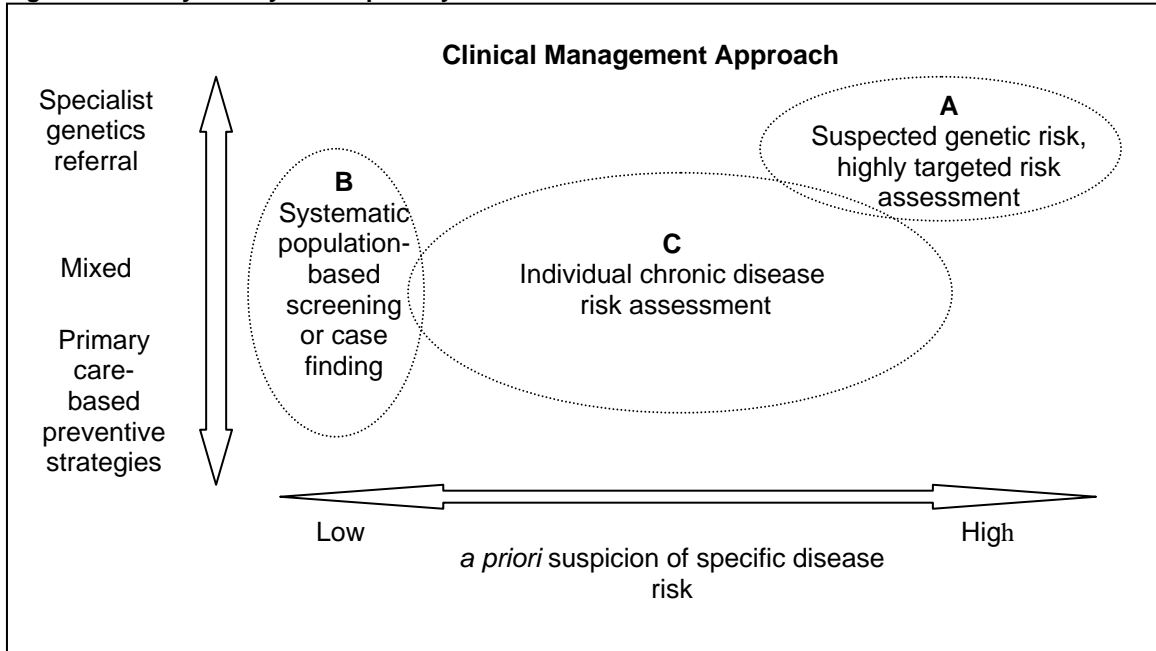
Cancer	≥1 IDR	≥2 IDRs	Age cut-off younger, older	Younger affected relative	Older affected relative
Colorectal	2.24 (2.06, 2.43)	3.97 (2.60, 6.06)	<50, ≥50	3.55 (1.84, 6.83)	2.18 (1.56, 3.04)
Breast	1.80 (1.70, 1.91)	3.01 (2.46, 3.69)	<40, >60	2.22 (1.71, 2.87)	1.55 (1.38, 1.74)
Ovarian	2.85 (2.41, 3.37)	14.74 (5.78, 37.60)	<50, ≥50	3.98 (2.53, 6.26)	2.90 (2.10, 4.01)
Prostate	2.42 (2.25, 2.60)	4.27 (3.13, 5.84)	<60, ≥60	2.91 (2.12, 4.01)	1.88 (1.47, 2.40)

IDR=first degree relative

These meticulous analyses provide direct evidence to support the association between family history and risk of cancer even when family history is captured in a less specific or extensive way than is the case in a specialist genetics consultation.

In order to understand the specific nature of family history information which might be most useful in primary care settings, it is useful to consider how family history data may serve different purposes. Figure 1 maps out different contexts for family history taking in primary care against the general locus of clinical management (primary care versus specialist referral) if elevated risk is identified. It demonstrates how the goal of family history taking may include, but is most definitely not limited to, identifying rare, high risk disease patterns in families which warrant referral for formal genetic evaluation (domain A). Domain B represents systematic screening of general patient populations for a defined range of familial or genetic diseases. Domain C represents the assessment of disease-specific family history information with other risk factor data in the assessment of chronic disease risks in individual patients. In all three domains (A, B, C), a primary care practitioner may be the key provider who captures the family history data; however, the drivers for capturing such information, and the likely decisions that will follow, vary across the three domains and extend beyond the possible identification of classical genetic disorders.

Figure 1: Family history-based primary care activities



Domain A represents the assessment of a patient in whom clinical suspicions of an inherited disorder or predisposition have arisen, for example in response to concerns about several relatives affected by cancer. In this situation, the main clinical goal would be to assess whether the individual met the criteria for referral for specialist genetics assessment and/or genetic testing. A family history ‘tool’ in this situation would be represented by guidelines for genetic referral or testing. Here, the focus would be on capturing specific family history information which might be rather extensive and specific, requiring attention to, for example, different combinations of diseases in the family, the lineage of affected relatives, and so forth, as illustrated in the Bethesda criteria for non-polyposis colorectal cancer.⁵⁶

Domain B might typically represent a periodic health assessment in an otherwise healthy individual, where there would be no suspicion of underlying genetic disease and no particular indications of illness or disease susceptibility. Here, the goal would be to conduct a broad brush assessment across a range of common disorders, to identify issues which warrant further probing by the primary care practitioner. The most useful family history tool might incorporate a limited range of the most sensitive family history markers or “red flags” across a range of disorders, in the expectation that more detailed information would be collected for those conditions where an indicator item was positive.

In domain C, the primary care practitioner’s goal would be to incorporate family history with other clinical and personal information to assess future risk of a specific chronic disease, with a view to ordering further investigations and advising on appropriate risk reduction strategies. In this situation, the focus would be on family history items which were either independently highly predictive of disease risk, or added useful incremental predictive value to other, established risk factors. A family history “tool” in this context might actually consist of a short set of questions within a more comprehensive disease-specific risk assessment guideline. An example of this approach would be the incorporation of information on parental history of myocardial infarction in the National Cholesterol Education Program III guidelines.⁵⁷

These three domains are clearly not mutually exclusive. However, this approach illustrates that the demands of extensiveness and specificity of the type of information that is necessary is not uniform across all contexts. Until comprehensive and current family history information is available for patients through, for example, electronic records systems, a primary care practitioner's approach to family history-taking may be influenced by external constraints (e.g., time), their prior assessment of the patient's risk of disease, and the way in which the information will actually be used for decisionmaking.

Although this report borrows from the language and concepts of genetics and genomics (see below), its approach reflects the perspective on family history exemplified particularly by domain C described above. Its focus is on the utility of using family history information to stratify the risk of common, complex diseases in individuals who are not specifically selected for suspicion of high genetic risk.

Evaluating Family History for use in the Prevention of Cancers

The usefulness of family history stratification systems as predictive tools for common, chronic diseases can be approached using an evaluation framework originally developed by the Secretary's Advisory Committee on Genetic Testing.⁵⁸ This framework has four elements (1) analytic validity; (2) clinical validity; (3) clinical utility; and (4) ethical legal and social implications of using a test. It has been further developed for application to the evaluation of family history information in disease prevention (see Table 2 for definitions).⁵⁹ Put another way, the line of evidence between family history and individual and population benefit requires answers to the following questions:

- (a) Does a positive family history (however defined) predict future risk of cancer in an individual patient sufficiently accurately to be useful in a clinical setting?
- (b) If so, are there interventions available which reduce the risk of cancer? Do these interventions also carry risks?
- (c) If there are interventions which help prevent cancer, does information on family history-based disease risk mean a person is more likely to adhere to them (compared with advice which is not based on knowledge of family history)?
- (d) Are there any direct harms which arise from the process of taking a family history and feeding back personalized risk based on family history?

In terms of efficient health care resource use, it is also legitimate to examine the incremental benefits and costs associated with capturing and using family history information, whether it substitutes for, or adds informational value to, other risk factor information, and whether it is easier and/or cheaper to obtain.

Table 2. Elements and key components of evaluation framework for family history as screening tool [reproduced from Yoon, Scheuner, and Khoury 2003]⁵⁹

Element	Definition	Components
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (disease status among relatives) that it is intended to measure	Analytical sensitivity Analytical specificity
Clinical validity	A measurement of the accuracy with which a test or tool identifies or predicts a clinical condition	Clinical sensitivity Clinical specificity Positive predictive value Negative predictive value
Clinical utility	Degree to which benefits are provided by positive and negative test results (presence and absence of family history for disease)	Availability of effective interventions Health risks and benefits Economic assessment
Ethical, legal, and social implications	Issues affecting data collection and interpretation that might negatively impact individuals, families, and society	Stigmatization Discrimination Psychological harms Risks to privacy and confidentiality

Yoon P.W., Scheuner M.T., Khoury M.J. Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med* 2003;23(2)128-135. Used with permission.

In a previous effectiveness report,⁵ evidence regarding the accuracy of reporting by individuals of their family history of breast, ovarian, colorectal, and prostate cancer was synthesized, and a large number of family history tools and family history-based risk assessment tools identified and reviewed. The current review is designed to inform issues (a) to (d) above, which address the issues of clinical validity and, in part, clinical utility.

Risk Stratification

A number of risk classification systems exist, generally in the form of guidelines or algorithms developed to assist in decisionmaking around referral to genetic services or genetic testing (e.g., Rodriguez-Bigas⁵⁶). Few risk stratification systems have been developed specifically for direct application in primary care, with a focus on recommending behavior changes and/or preventive clinical interventions in which referral for genetic counselling would be relevant for only a small sub-group of patients. One such system is that proposed by Scheuner and colleagues⁶⁰ who, in a paper predating Butterworth's analysis,³ used available epidemiological data⁶¹⁻⁷⁰ to define three risk strata for a number of complex disorders (Table 3). An approach like this has the merit of appearing practical for immediate and easy application in primary care settings, but further evaluation is necessary to determine its predictive ability for the disorders of interest (clinical validity).

Table 3. Family history-based risk stratification guidelines for breast, ovarian, colorectal, prostate cancers⁶⁰

High risk
<ol style="list-style-type: none"> 1. Premature disease* in a 1DR 2. Two affected 1DRs 3. A 1DR with late/unknown onset of disease and an affected 2DR with premature disease from the same lineage 4. Two 2DRs, maternal or paternal, with at least one having premature onset of disease 5. Three or more affected maternal or paternal relatives 6. The presence of a 'moderate risk' family history on both sides of the pedigree 7. Pedigree demonstrating clustering of different primary cancers consistent with a family cancer syndrome
Moderate risk
<ol style="list-style-type: none"> 1. A 1DR with late or unknown disease onset 2. Two 2DRs from the same lineage with late or unknown disease onset
Average (population) risk
<ol style="list-style-type: none"> 1. No affected relatives 2. Only one affected 2DR 3. No known family history 4. Adopted individual with unknown family history

Scheuner M.T., Wang S.J., Raffel L.J., Larabel S.K., Rotter J.I. Family history: a comprehensive genetic risk assessment method for the chronic conditions of adulthood. *Am J Med Genet* 1997;71(3):315-324. Used with permission of John Wiley & Sons, Inc. Abbreviations: 1DR=first degree relative; 2DR=second degree relative

*Breast, ovarian: premenopausal or ≤ 50 years; colorectal, prostate ≤ 50 years

Effectiveness of Cancer Risk Reduction Interventions

Even the most highly predictive and practical risk stratification system cannot change health outcomes unless effective cancer prevention interventions are available for patients at risk. While there is extensive epidemiological literature on a wide range of cancer risk factors, much of the evidence regarding cancer prevention is based on observational studies. Contradictory evidence has emerged when some apparently protective factors, identified through observational studies⁷¹⁻⁷³ were associated with increased risk of cancer in experimental studies, as was the case for alpha-tocopherol.⁷⁴ It is crucial that any assessment of the clinical utility of family history-based risk stratification take into account the highest quality evidence on the benefits and risks of recommended preventive interventions.

Effect of family history taking on uptake of interventions. Assuming that proven preventive interventions are available, the question remains whether individualized, family history-based advice actually promotes uptake of such interventions by patients. Simplistically, it might be assumed that individuals would be more motivated to act on a health care provider's advice if they know they are at higher than average risk. However, there is a body of literature in the area of predictive and predisposition genetic testing which cautions that knowledge of genetic risk might lead to fatalism in those at higher risk (failing to take up available interventions because of the 'inevitability' of disease) or complacency in those at average risk (failing to take up available interventions because of lower perceived personal risk - the 'certificate of health' effect).⁷⁵ Like any healthcare intervention, family history taking may incur incremental costs in time, energy, and money over and above standard care, therefore an examination of the incremental benefits is important.

Risks inherent in family history-based risk assessment. No healthcare intervention should be assumed to be safe without formal assessment of harms as well as benefits. While family history taking is seen as a standard activity in all areas of healthcare, the systematic capture of

more extensive information, and its purposeful use in individual risk assessment, merits objective review. The ACCE framework⁵⁸ emphasizes the assessment of both harms and benefits, and there is substantial literature that examines the impacts of predictive genetic tests beyond simple accuracy.⁷⁶ While some guidelines⁷⁷ suggest a cautionary approach, with cancer family history collection undertaken only in response to patients' enquiries, many other observers argue that family history taking is an integral part of good clinical practice.^{78,79} Objective evidence on the prevalence of specific harms of family history taking, and of its use in advising patients about disease risk reduction, is necessary in order to clarify the appropriate level of caution to be exercised, and the types of situations in which patients might be most vulnerable to potential harms.

Scope and Purpose of the Systematic Review

This report is intended to build on a published evidence report focused on collection and use of family history for breast, ovarian, colorectal, and prostate cancers.⁵ The key questions for that project are available at: <http://www.ahrq.gov/clinic/tp/famhisttp.htm>. The current systematic review addresses four key research questions relating to the clinical validity and utility of routinely using family history information in risk assessment and prevention of breast, ovarian, colorectal, and prostate cancer in primary care, as follows:

1. Which risk stratification algorithms or guidelines delineate risk accurately, and in a clinically meaningful way?
2. For which behaviors and clinical preventive services ('interventions') is there evidence of benefits in terms of actual reduction in disease risk, and what harms, if any, have been identified?
3. For those interventions identified as being based on reasonable evidence, what is the evidence that providing information on risk status results in behavior change or increased uptake of services on the part of individual patients?
4. What are the harms or risks to individual patients that may result from the collection of family history information in itself, and/or the provision of family history-based risk information?

Addressing these four key questions requires a focus on different types of evidence and different sets of literatures. The focus of key question (Q1) is not only on identifying family history-based risk prediction systems (which may be presented as guidelines, algorithms or other tools) suited to use in primary care, but also on assessing their actual predictive ability when applied to individual patients. This requires review of primary studies addressing discriminatory accuracy in cohorts representative of relevant general populations. Key question (Q2) asks whether effective cancer prevention interventions are available. While answering this question is an essential step in addressing the overall question of clinical utility of cancer family history taking, we note that the primary goal of this report is on family history taking, rather than evidence for cancer control *per se*. Given the considerable practical implications in attempting to synthesize the very extensive literature on cancer risk factors and prevention (see, for example, the reports by the World Cancer Research Fund^{26,45,46}), the reasonable expectation that evidence reviews might be available for cancer prevention interventions which are considered standard of care, and direction from the sponsors of the report, the focus is therefore on reviewing systematic

reviews for primary and secondary (screening) cancer prevention. Key questions (Q3) and (Q4) are evaluative questions. Question 3 asks whether taking and using family history information is more likely to lead to desired behavior changes in patients than other approaches which do not use family history information. In addressing this question it is important to distinguish between studies which examine the behavior of people who have pre-existing perceptions of elevated disease risk because of living with a “family disease” from the *clinical strategy* of systematically capturing family history information and personalizing risk assessment for all patients, in order to promote adherence to recommended preventive behaviors. The possibility for confounding of the latter by the former cannot fully be addressed in observational studies, and steers the review towards examining evidence from well-designed intervention studies. The same issue applies in question (Q4), where adverse outcomes from the clinical strategy of taking and using family history information needs to be separated out from the psychological and social impacts of living with the implications of pre-existing *perceived* familial disease risk.

As discussed above, the focus of this review is firmly on using family history information in a primary care context. This has driven the eligibility criteria for studies towards

- study populations that resemble those in primary care – with an inherent range of disease risks but not selected because of suspicion of genetic disease
- study settings where primary care providers such as family physicians, internists, nurse practitioners, and obstetricians are taking family histories and assessing risk
- family history taking as an intervention carried out by primary care practitioners and directed primarily towards chronic disease risk assessment and prevention as an end in itself
- cancer prevention interventions evaluated in primary care or general populations with an inherent range of disease risks, but *not* selected because of special high risk (genetic or otherwise)

Even within primary care, we recognize that there is an inevitable gradation (rather than a clear cut separation) between family history taking as a means to promote effective primary care-based disease risk assessment and management (domain C, Figure 1), and family history taking as a way of identifying individuals who may be at high genetic risk, where referral to specialist genetics services is warranted (domain A). We therefore sought to include studies examining family history taking as a generalist activity, and to exclude studies which focused on family history as part of a clinical genetics assessment. Thus, even though we recognize that family history taking is a core activity in specialist genetics, this review excludes literature where the focus is primarily on the assessment of genetically high risk patients in specialist settings.

It is also important to emphasize that the focus on study populations “unselected” for high risk implies groups of participants which represent *a full range of risks*, potentially from very low to very high, with clustering around an “average” value (by definition). This criterion was adopted in an effort to reflect professional and patient decisionmaking in “typical” primary care contexts where patients with a wide range of risks (but mostly “average”) are encountered. Thus, it would be expected that a predictably small proportion of patients from an unselected population would be classified by a risk stratification system into a high risk category. This situation is distinctly different from those where patients and their providers already know or suspect that they are at high disease risk, by virtue of, for example, an uncommon pattern of familial disease, a positive genetic test result in a close relative, a previous diagnosis of the condition, or diagnosis of a pre-disease state. In short, populations unselected for high risk may *include some high risk individuals* whereas populations selected for high risk definitively *exclude*

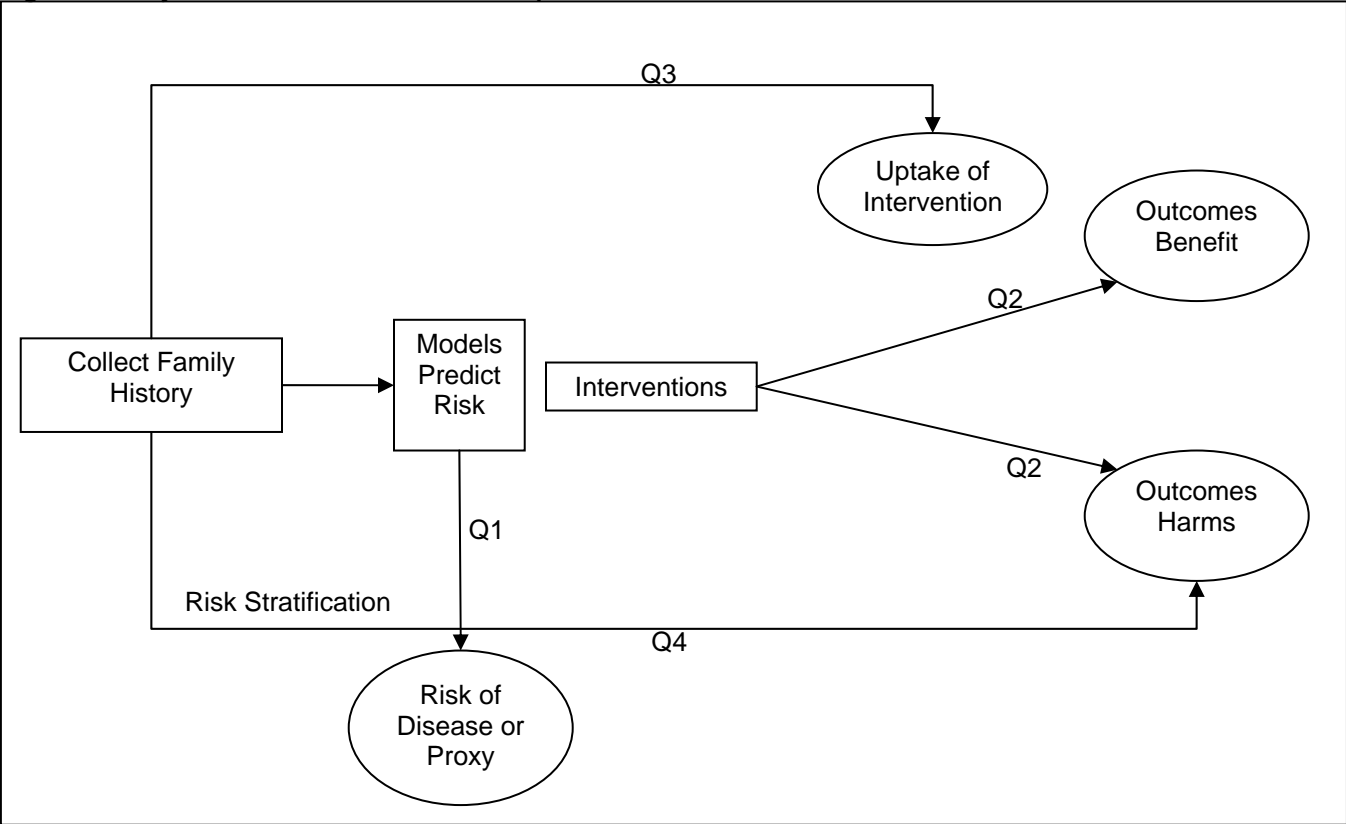
average and low risk individuals. We suggest that it cannot be assumed that findings from “selected for high risk” studies are directly applicable to the general primary care context.

Chapter 2. Methods

Analytic framework

The analytic framework is a schematic representation of the strategy for showing the relationships between the primary exposure, which is the collection of cancer family history, and the outcomes of interest for each research question. Figure 2 shows the inter-relationships among the four research questions being addressed in this systematic review. Cancer family history is an important component of algorithms, models, and guidelines used to predict risk of cancer or gene mutation; we evaluated predictive accuracy outcomes of eligible algorithms, models, or guidelines in the first research question (Q1). A large number of interventions have been implemented to address primary and secondary prevention of the cancers of interest; our second research question evaluated the evidence from systematic reviews and evaluated outcomes of benefit and harm from these interventions (Q2). Following the collection of cancer family history, the uptake of these prevention and screening interventions was the outcome of interest for our third research question (Q3). Our final research question focused on the potential for harmful outcomes as a result of collecting family history (Q4).

Figure 2. Analytic framework for the research questions evaluated in this review



Search Strategy

Bibliographic databases searched for this review included: MEDLINE®, EMBASE®, CINAHL®, Cochrane Controlled Trials Register (CCTR)® (Q1, Q3, Q4), Cochrane Database of Systematic Reviews (Q2), and PsycINFO (Q3). Years searched were 1990 to June 2008 inclusive (Q1, Q3, and Q4). We searched for cancer guidelines and recommendations from 2002 forward to ensure that the guidelines were reasonably current. We also searched the grey literature, including the National Clearing House for guidelines. Based on input from our Technical Expert Panel we searched the Guide to Community Preventive Services published by the CDC⁸⁰ and other appropriate guidelines (e.g., U. S. Preventive Services Task Force recommendations for the prevention and screening interventions for the cancers of interest).

Finally, we restricted the search for systematic reviews (Q2), from 2003 to June 2008 (Q2). As per the recommendations of our content experts, we reviewed the methods and content of the report “Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective” published by World Cancer Research Fund’ from American Institute for Cancer Research (updated for breast cancer only in Spring 2008).⁸¹ This report reflects an international initiative that has systematically reviewed the literature to evaluate the cancer prevention evidence for a range of interventions broadly including exercise and related behaviors, food and food supplements (including vitamins), and screening interventions for different types of cancer (including breast, ovarian, colorectal, and prostate cancers). Since this World Cancer Review comprehensively captured and evaluated the literature on these interventions from root to the end of 2006), we did not include any reviews on these particular interventions for this time period.

In addition we retrieved and evaluated references from eligible articles. Hand searching was not undertaken, but we reviewed the publication type “letters” (normally excluded from reviews); the investigators suggested that, within the content area of cancer genetics, primary data information might be published as letters in some journals. Finally, we formally reviewed all articles suggested by peer reviewers of the draft evidence report and incorporated those which met eligibility criteria. Detailed search strategies are listed in Appendix A.

Eligibility Criteria

A list of eligibility criteria was determined and standardized forms were developed in Systematic Review Software (SRS, 3.0, TrialStat Corporation, Ottawa, Ontario Canada) and Microsoft Excel for the purposes of this systematic review.

Publication Year, Type, and Language

Inclusion

Language: Only English language studies were eligible. (Q1, Q2, Q3, Q4)

Publication Date: 1990 to June 2008. (Q1, Q3, Q4)

2003 to June 2008 (Q1 guidelines/recommendations and Q2)

Exclusion

Publications that were editorials, comments, opinions, or abstract only (Q1, Q2, Q3, Q4)

Eligibility Criteria for Research Q1:

Population

Any patient or general populations not selected for known or suspected pre-existing elevated risk of breast, ovarian, colorectal, and/or prostate cancer

Inclusion

- populations sampled from clinical settings, including population screening programs
- participants in analytical epidemiological research studies

Exclusion

- people with a personal history of breast, ovarian, colorectal, or prostate cancer
- people at high risk of cancer, as estimated by an existing risk assessment system
- populations sampled from specialist genetic clinics or cancer family clinics
- people who have had a genetic test for a mutation related to one of the cancers of interest (irrespective of result)

Intervention

Inclusion

Any system designed

- to use family history information alone, or in combination with other information typically and universally available to primary care practitioners (i.e., personal/demographic factors, past medical history, clinical observations that do not require specialist referral)
- to stratify people into two or more risk categories OR to provide a numerical point estimate of risk of developing breast, ovarian, colorectal, and/or prostate cancer, over any time period
- for application in risk assessment of individual patients
- in which the model validation is tested on a patient sample different than the one used to develop the model

Exclusion

- Systems which do not incorporate family history information
- Systems which include data from specialist investigations which are typically unavailable in primary care settings

Design

Inclusion

1. Analytical studies examining disease risk categorization as the 'exposure' and cancer incidence or proxy as the 'outcome'
 - cohort (prospective or historical)
 - case control
2. Diagnostic studies examining disease risk categorization using the algorithm as the 'test' and cancer incidence or proxy as the 'reference'
3. Intervention studies examining disease risk classification system as the 'intervention' and correct prediction of cancer incidence or proxy as the 'outcome'
 - randomized controlled trials (cancer risk classification system compared with any other system, or no system)

- non-randomized controlled trials (cancer risk classification system compared with any other system, or no system)
- uncontrolled before-after studies (data on prediction of patients' cancer risk before and after the introduction of a cancer risk classification system)

Exclusion

None

Outcome

Inclusion

1. Model calibration, expressed as observed versus expected cases
2. Model discriminatory accuracy, expressed as sensitivity, specificity, predictive value, likelihood ratio, concordance statistic, receiver operator characteristics (ROC), area under the curve (AUC), or other appropriate summary statistic

For the outcomes of

- incidence of breast, ovarian, colorectal, or prostate cancer
- breast-, ovarian-, colorectal-, or prostate-specific mortality
- proxies - incidence of known precancerous states, such as colorectal adenomatous polyps

Over any defined time period

Exclusion

None

Eligibility Criteria for Research Q2

Population

Inclusion

Reviews where eligibility criteria include AND outcome data are presented separately for:

General population, primary care patients or participants in population screening programs who may or may not have been selected by age and sex criteria but not on the basis of *a priori* higher risk, such as:

- personal history of cancer
- known precancerous condition
- known disorder which increases cancer risk
- known or suspected familial cancer syndrome

Participants may have had relatives with cancer, but they are not selected specifically on the basis of suspected genetic risk

Exclusion

Reviews where the eligibility criteria focus specifically on people eligible for, or who have had, a genetic test for a cancer-associated mutation (irrespective of result)

Intervention

Inclusion

Breast

- breast self-examination
- clinical examination
- screening mammography

- chemoprevention
- magnetic resonance imaging breast screening (MRI)
- referral for genetic counseling +/- genetic testing, where criteria are met

Colorectal

- fecal occult blood (FOB) test
- screening colonoscopy
- screening sigmoidoscopy
- chemoprevention
- referral for genetic counseling +/- genetic testing, where criteria are met

Ovarian

- ultrasound screening
- referral for genetic counseling +/- genetic testing, where criteria are met

Prostate

- prostate-specific antigen (PSA) screening
- digital rectal examination
- chemoprevention
- referral for genetic counseling +/- genetic testing, where criteria are met

General behaviors for all four cancers

- vitamins, minerals, micronutrient supplementation
- regular exercise/physical activity
- high fiber diet
- increased fruit and vegetable consumption or specific food intake
- low fat diet
- smoking cessation
- reduction in alcohol intake
- seeking healthcare advice
- participation in recommended screening/surveillance

Exclusion

None

Comparator/Study Design

Inclusion

Systematic reviews of primary studies which seek to identify studies with the following designs

- randomized controlled trials
- non-randomized controlled trials
- uncontrolled before-after studies (or non-controlled trials)

Comparators:

- as reported in primary studies

Exclusion

Systematic reviews of primary studies which focus solely on the following designs

- cohort studies
- case-control studies
- case series and case reports

Outcomes

Inclusion

- cancer incidence
- cancer-related mortality
- all cause mortality
- incidence of known precancerous conditions
- complications of diagnosis, complications or side effects of treatment, psychosocial sequelae

Exclusion

All other outcomes

Eligibility Criteria for Research Q3

Population

Any patient or general populations not specifically selected for known or suspected pre-existing elevated risk of breast, ovarian, colorectal, and/or prostate cancer

Inclusion

- populations sampled from population or clinical settings, including population screening programs

Exclusion

- populations selected entirely on the basis of a personal history of breast, ovarian, colorectal, or prostate cancer
- populations selected entirely on the basis of having a high risk of cancer, as estimated by an existing risk assessment system or a genetics specialist
- populations sampled from specialist genetics clinics or cancer family clinics
- populations selected entirely because they have had a genetic test for a mutation related to one of the cancers of interest (irrespective of the result)

Intervention

Inclusion

Systematic provision of personal risk of breast, colorectal, prostate and/or ovarian cancer based on family history, *alone or combined with* individual advice on appropriate risk reduction behaviors and/or services

Exclusion

- family history taking without provision of personal risk information
- advice on risk reduction not accompanied by, or based on, family history information
- provision of general risk information
- genetic counseling

Comparator/Study Design

Inclusion

Primary studies of the following study designs:

- randomized controlled trials
- non-randomized controlled trials
- uncontrolled before-after studies (or non-controlled trials)

Comparators:

- no comparator group
- comparator group with no intervention
- comparator group receiving preventive advice without provision of family history-based information

Exclusion

- cohort studies
- case-control studies
- case series and case reports

Outcomes

Inclusion

- change in target behaviors related to cancer prevention, considered standard advice at the time of the primary study
- uptake of services identified in (Q2) or considered current/standard of care at the time of the primary study

Exclusion

None

Eligibility Criteria for Research Q4:

Population

Any patient or general populations not specifically selected for known or suspected pre-existing elevated risk of breast, ovarian, colorectal, and/or prostate cancer

Inclusion

- populations sampled from population or clinical settings, including population screening programs

Exclusion

- populations selected entirely on the basis of a personal history of breast, ovarian, colorectal, or prostate cancer
- populations selected entirely on the basis of having a high risk of cancer, as estimated by an existing risk assessment system or a genetics specialist
- populations sampled from specialist genetics clinics or cancer family clinics
- populations selected entirely because they have had a genetic test for a mutation related to one of the cancers of interest (irrespective of the result)

Intervention

Inclusion

Systematic collection of family history information and/or the provision of family history-based personal risk of breast, colorectal, prostate, and/or ovarian cancer

Exclusion

- advice on risk reduction not based on family history information
- provision of general risk information
- genetic counseling

Comparator/Study Design

Inclusion

Primary studies of the following study designs:

- randomized controlled trials
- non-randomized controlled trials
- uncontrolled before-after studies (non-controlled trials)

Comparators:

- no comparator group
- comparator group with no intervention
- comparator group with intervention not based on family history collection or family history-based preventive advice

Exclusion

- cohort studies
- case-control studies
- case series and case reports

Outcome

Inclusion

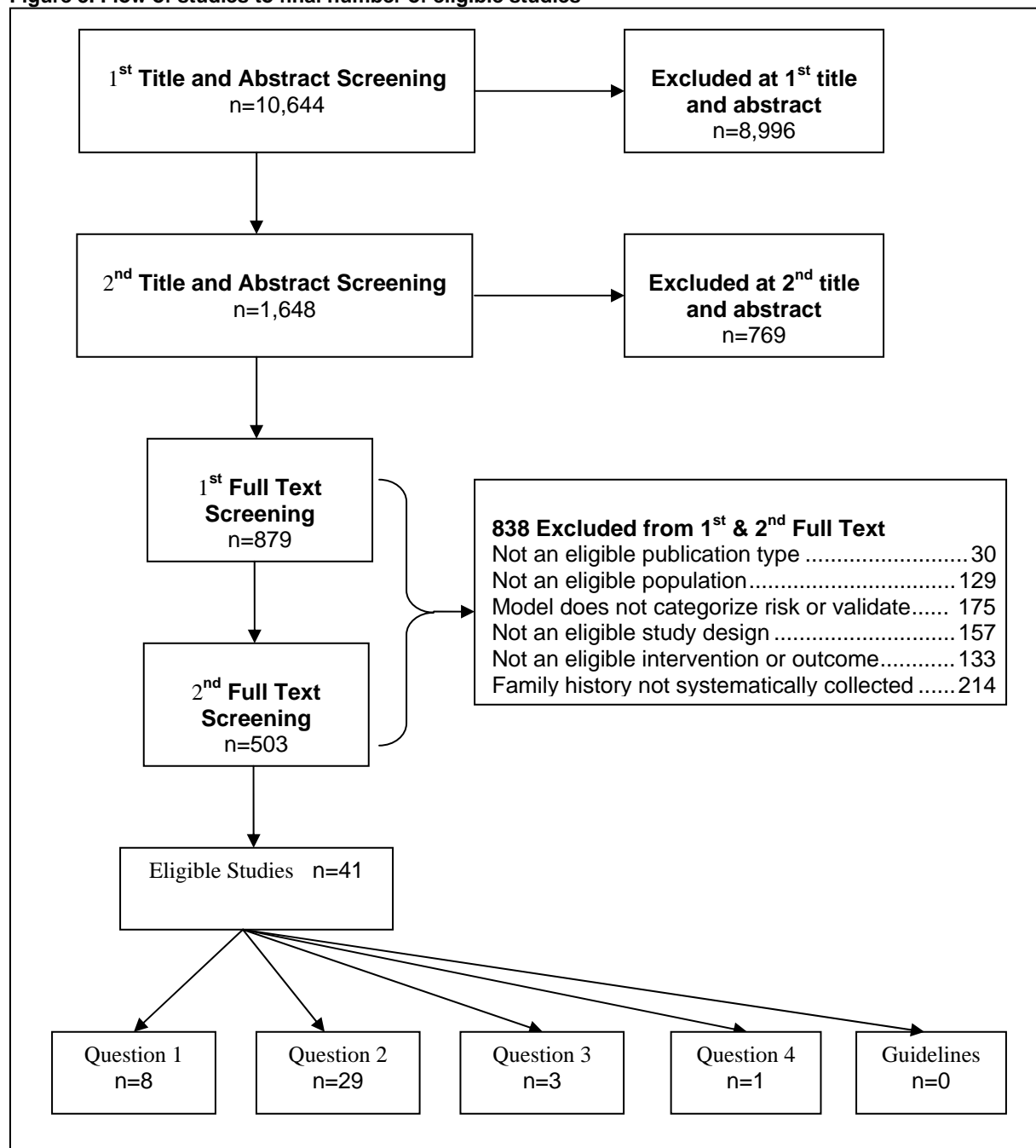
- psychological status
 - anxiety/distress
 - cancer worry
 - depression
 - inaccurate risk perception
 - other psychological outcome
- quality of life
- social impacts
 - family functioning including dynamics/communication, etc.
 - insurance or employment discrimination
 - other

Exclusion

- outcomes not listed above

Figure 3 illustrates the flow of studies based on the eligibility criteria described.

Figure 3. Flow of studies to final number of eligible studies



Study Selection

A team of study assistants was trained to apply the eligibility criteria for screening the title and abstract lists and the full text papers. All levels of screening were done in web-based Systematic Review Software (SRS) (TrialStat Corporation, Ottawa, Ontario Canada). Standardized forms and a training manual explaining the criteria were developed and reviewed with the screeners (Appendix B). For the title and abstract phase, two reviewers evaluated each

citation for eligibility. Articles were retrieved if either one of the reviewers judged it as meeting eligibility criteria or if there was insufficient information to determine eligibility. For screening of full text articles, two screeners came to consensus on the identification, selection, and abstraction of information. Disagreements that could not be resolved by consensus were resolved by one of our McMaster research team members.

Data Extraction

Appropriate data collection forms were developed for use in the SRS (Appendix B). All eligible studies from the selection phase (full text screening) were abstracted onto a data form according to predetermined criteria. One data extractor transferred the data onto these forms, and another checked the answers for accuracy before they were entered into SRS. Data entries were verified by the investigators responsible for summarizing the different report results sections.

Quality Assessment and Peer Review

Quality assessment of studies was undertaken in varying forms. Studies eligible for (Q1) were evaluated for potential bias in relation to the model variables and selection bias. For the systematic reviews identified for (Q2), a modified version of the Oxman-Guyatt Overview Quality Assessment Questionnaire, a validated, 10-item assessment scale was used.⁸² Studies for (Q3 and Q4) were evaluated using the Jadad scale for randomized trials.⁸³

A draft version of this report was circulated to 14 peer reviewers (see Appendix E). Where possible, comments and suggestions were incorporated.

Summarizing our Findings: Descriptive and Analytic Approaches

A qualitative descriptive approach was used to summarize study characteristics and outcomes. Multiple publications on the same study cohort were grouped together and treated as a single study with the most current data reported for presentation of summary results. Standardized summary tables explaining important study population and population characteristics, as well as study results, were created. Meta-analysis was not undertaken for eligible studies for (Q1, Q3, or Q4) as the clinical heterogeneity between studies was considerable.

Chapter 3. Results

Our comprehensive search yielded 10,644 unique citations; from these 9,765 were excluded as they were not an English language publication, not on the cancers of interest, or on topic for any of the four research questions (Figure 3). The remaining 879 citations were screened at full text and of these a total of 12 primary studies and 29 systematic reviews were eligible for inclusion in this review.

Research Q1: Which Risk Stratification Algorithms or Guidelines Delineate Risk Accurately, and in a Clinically Meaningful Way?

General Approach

We reviewed published studies which examined the ability of models (or algorithms, or guidelines) which used family history information to accurately predict individual risk of breast, ovarian, colorectal, or prostate cancer. To be eligible, the model had to include systematic collection of specified family history information, either alone or with other personal or clinical information which would be available for all patients and routinely available to a primary care practitioner. We examined the performance of models in relation to populations not selected for known or suspected high risk of cancer.

Model performance was assessed by predictive accuracy, in terms of calibration and discrimination. “Calibration” is a model’s ability to correctly predict the number of observed events (incidence of cancer) in a population and is generally evaluated by its goodness-of-fit to observed events. The ratio of observed to expected cases provides an overall epidemiological assessment of how well a model might perform for a defined population.

“Discrimination” is the assessment of how well a model separates out individuals who will go on to develop different outcomes. Discriminatory accuracy for dichotomous outcomes (e.g., disease/no disease) is best examined through metrics such as sensitivity and specificity, predictive value, likelihood ratio, and the area under the receiver operator characteristic (ROC) curve (or area under the curve (AUC)). The AUC is also referred to as the c-statistic and is defined in the unit square with a range of 0 to 1.0. Since chance alone will follow a perfect diagonal from (0,0) to (1,1), the subsequent AUC will be 0.5 (no apparent discrimination), whereas an AUC of 1.0 indicates perfect discriminatory accuracy.

Discriminatory accuracy is a more relevant evaluation than calibration from the point of view of clinical practice, as it directly indicates how well the model predicts an individual patient’s likelihood of developing cancer within a defined time scale. A model that is well calibrated at a population level may not necessarily be highly discriminating when used for individual prediction.

Studies Reviewed

Eight evaluation studies were retained for data abstraction after full text review.⁷⁻¹⁴ All except one focused on breast cancer risk assessment. The individual breast cancer models were

all conceptually related: the “original” Gail model,¹⁵ the modified Gail model,⁸⁴ the modified Gail model for African American populations,¹⁰ the modified Gail model for Italian populations,^{11,12} and the model developed from the Contraceptive and Reproductive Experiences (CARE) study.⁷ The exception was Harvard Cancer Risk Index (HCRI),¹⁶ which was developed for calculating the risk of a several cancers, including breast, ovary, colon, and prostate. An eligible validation¹⁴ of the HCRI was published only for colon cancer.

The details of the models are summarized in Table 4. All of the models examined used a set of predetermined input variables in addition to family history as the basis for risk assessment. These variables included a range of personal demographic and disease-specific risk factors such as age, ethnicity, reproductive factors, diet, history of clinical investigations (e.g., breast biopsies, colonoscopies), and other risk factors such as body mass index, and alcohol consumption.

Outcomes

The details of evaluations of the models are summarized in Table 5. All evaluations were performed as secondary analyses of data derived from observational studies or trials. The sample sizes for the evaluations ranged from 1,450 to 147,916, covering a wide age range of participants. Six of the evaluations^{7-10,13,14} were conducted in U.S. populations: the Nurses’ Health Study (NHS)^{14,85,86} (4 studies), the Women’s Health Initiative (WHI)^{7,87} (2 studies), the Black Women’s Health Study,⁸⁸ and the Health Professionals Follow-Up Study (HPFS).⁸⁷ The remaining two evaluations^{11,12} were conducted in Italian populations. Followup periods in the validation cohorts ranged from 5 to 10 years.

Gail Model

The first published version of the ‘Gail Score’¹⁵ used information on a woman’s age at menarche, her age at the time of the birth of her first child, the number of her first degree relatives who had had breast cancer, and the number of previous breast biopsies that she had undergone. It was designed for women with no personal history of breast cancer who were being followed by annual screening mammography. It estimates the absolute probability of developing invasive or in situ breast cancer over a defined age interval. The model uses estimates of baseline hazard and attributable risk derived from the Breast Cancer Detection Demonstration Project (BCDDP).⁸⁹ The authors indicated that its primary application would be to “determine eligibility for entry to breast cancer prevention trials, where an important determinant of sample size is the absolute risk of breast cancer” in the study population.¹⁵

We identified a single study⁸ which evaluated the original Gail model,¹⁵ a secondary analysis of data from the NHS.^{85,86} The ratio of expected to observed breast cancer cases was 1.33 (95 percent CI 1.28-1.39), which was a significant overestimation. Only modest discriminatory accuracy was demonstrated (Pearson correlation coefficient 0.67).

Modified Gail Model

The modified Gail model incorporated revisions to improve its validity and applicability to the North American population.⁸⁴ The key revisions were a focus on the absolute risk of invasive breast cancer only (i.e., in situ cancer was excluded): the inclusion of a diagnosis of atypical

hyperplasia on biopsy as an additional risk factor; and the substitution of age-specific invasive breast cancer rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) for the BCDDP-based data used in the original model.

We identified five studies which evaluated the performance of the modified version of the Gail model, either in its originally published form, or adjusted to take account of different underlying breast cancer incidence patterns in different populations (African American,¹⁰ Italian^{11,12}). The ratios of expected to observed invasive cancer cases ranged from 0.79 to 0.96, mostly not statistically significantly different from unity. Validations, performed in a predominantly white U.S. population⁹ and two Italian populations,^{11,12} suggested reasonably good calibration, but poorer performance in “more diverse”¹³ and African American¹⁰ U.S. populations. These studies all suggested that the standard and modified versions all had very modest discriminatory accuracy (concordance statistic 0.58-0.59).

CARE Model

The CARE Model⁷ was developed as an African American adaptation of the Gail model, using data from the Women’s Contraceptive and Reproductive Experiences (CARE) Study,⁹⁰ the SEER program, and National Center for Health Statistics. It is a simpler model, in that two variables in the modified Gail model were removed and one was dichotomized.

We identified one study that validated this model, in a subset of African American women in the WHI. The model showed good calibration, with an expected observed ratio of cases not statistically significantly differently from unity. The discriminatory accuracy, expressed as AUC, was 0.555, which suggests only very modest predictive ability at best.

The authors compared the CARE Model with the MGM in classifying eligibility for a chemoprevention trial, and found that it doubled the proportion of women who met inclusion criteria (30.3 percent compared with 14.5 percent).

Harvard Cancer Risk Index

The HCRI was developed as a tool to assist clinicians in counseling patients about cancer risk reduction.¹⁶ It addressed prediction of the most common cancers in American men and women (prostate, breast, lung, colon, bladder, endometrium, non-Hodgkin’s lymphoma, ovary, kidney, leukemia, cervix, pancreas, skin melanoma, and stomach). The tool was developed using a consensus-based process in which available evidence was used to assign points for different levels of defined risk factors. Risk was stratified into a seven point categorical scale, set relative to the average U.S. population risk for each cancer. Several risk factors contributed to the score for each cancer, family history being included in all except leukemia and cervical cancer.

We identified one validation study,⁸⁷ in which the HCRI’s predictive validity for colon cancer was assessed in two cohorts, the NHS (women) and the HPFS (men). Results pertaining to ovarian cancer were also reported in this publication, but family history items were lacking, therefore these data were excluded from the current review. In addition to family history, eight variables for men and eleven for women were included in the HCRI for colon cancer.

The overall ratios of observed and expected cases were not reported. For women, the ratios by initial risk stratum ranged from 0.58 to 1.79, and for men 0.75 to 2.35. A better fit was observed for women than men. The AUC was 0.67 for women and 0.71 for men, suggesting moderately good discriminatory accuracy.

Conclusion

There were essentially two families of tools on which relevant performance data were available, those based on the Gail model, and the HCRI. None of the identified studies evaluated the performance of a predictive tool or algorithm, designed for use in populations not already pre-selected for higher risk, and *using family history information alone*. No validation studies of tools designed for risk prediction for ovarian or prostate cancer were found.

Most, but not all models demonstrated good calibration for the populations for which they were developed. However, none of the models identified demonstrated more than moderate ability to correctly discriminate risk at an individual level. The highest concordance presented was 0.71: this is equivalent to the correct classification of future disease (present or absent) in 71 percent of individuals, and incorrect classification of 29 percent.

Research Q2: For Which Behaviors and Clinical Preventive Services is There Evidence of Benefit in Terms of Actual Reduction of Disease Risk, and What Harms, if any, Have Been Identified?

General Approach

For the purposes of this review, we included published quantitative and qualitative reviews of the effectiveness of personal behavioral/lifestyle and clinical interventions that are commonly recommended as part of cancer risk reduction strategies in primary care settings. The list of interventions of interest was developed by the study team in consultation with the partners and the members, and was incorporated into the eligibility criteria for the review. Table 6 lists the interventions of interest.

Where multiple reviews addressing the same intervention were identified, they were scrutinized to determine the degree of overlap, as well as for quality. We selected the most recent and/or most comprehensive review for reporting, bearing in mind any differences in quality.¹⁷

Studies Reviewed

Twenty-nine systematic reviews fulfilled eligibility criteria after full text review. These eligible reviews addressed evidence for four chemoprevention interventions (antioxidant supplementation, calcium supplementation, non-steroidal anti-inflammatory drugs (NSAIDs), in the form of aspirin, but not COX-2 inhibitors and statins) and five screening interventions (breast self-examination (BSE), screening mammography, fecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), and prostate specific antigen (PSA), for three cancers (breast, colorectal, and prostate).

No reviews were identified which examined evidence for magnetic resonance imaging in breast screening, ultrasound ovarian screening, colonoscopy as a stand-alone screening intervention, regular exercise, dietary interventions other than supplements (reviewed under chemoprevention), reduction in alcohol consumption, smoking cessation, seeking health care advice or referral for genetic counseling and/or genetic testing. As mentioned in chapter 2, we

did not search for reviews for food, nutrition or physical activity interventions before 2006 as these were well evaluated in the World Cancer Research Fund/ American Institute for Cancer Research Second Expert Report.⁸¹

Of the eligible studies, data were extracted from the 10 reviews which represented the most comprehensive, up-to-date, and high quality evidence.¹⁸⁻²⁷ Twelve additional reviews reported overlapping data²⁸⁻³⁹ but these data were not extracted. Five reviews⁴⁰⁻⁴⁴ did not identify primary intervention studies despite being designed to do so; and two reviews^{45,46} identified apparently relevant intervention studies but did not report usable data. The studies, which were not reported, on are listed in Table 1 in Appendix C.

The findings of the reviews which were included and reported are presented in Tables 7, 8, and 9. Some reviews addressed evidence related to prevention of more than one cancer type; in this situation, the results are presented separately by cancer type.

Breast Cancer

Five reviews on breast cancer prevention¹⁸⁻²² are presented in Table 7 which synthesizes evidence in relation to chemoprevention (antioxidants and statins), screening (BSE), and screening mammography.

Chemoprevention. ‘Chemoprevention’ refers to the use of chemical compounds to arrest or reverse the earliest stages of carcinogenesis or development of pre-cancerous lesions. We apply it very broadly in this review to include the use of both recognized pharmaceutical agents (drugs) and supplements of naturally occurring elements and compounds administered in doses above those naturally encountered in typical diets, and/or administered in tablets or capsule.

Antioxidants. Antioxidants are molecules which inhibit or prevent damage to cells caused by oxidizing agents such as oxygen free radicals. It is suggested that such damage (oxidative stress) is an important early step in the development of many diseases, including cancer. It is hypothesized that antioxidant compounds could act as cancer prevention agents by preventing or inhibiting DNA damage, the earliest stage of carcinogenesis. Many observational epidemiological studies have found an inverse relationship between consumption of foods with high antioxidant content, such as fruits and vegetables, and incidence of cancer.⁷¹⁻⁷³

Antioxidants are a diverse group of compounds and different reviews have assessed them collectively and individually. Among the many antioxidants associated with food, the most commonly studied are vitamins (A, C, and E), their precursor molecules (e.g., alpha-tocopherol and β-carotene), and minerals (e.g., selenium and zinc).

We report the findings of two reviews that examined antioxidants and breast cancer incidence. The first review¹⁸ evaluated supplements which contained any combination of β-carotene, vitamin C, vitamin E, selenium, zinc, and other antioxidants, and the second review¹⁹ focused on vitamin E in any combination. Both of these reviews also evaluated outcomes related to colorectal and prostate cancer, the results for which are presented in the relevant sections below.

The first review¹⁸ included only placebo-controlled trials where antioxidants were given as supplements where the ingredients were fully disclosed, and which had followed up participants for at least one year. Their breast cancer analysis was based on 1,753 cancers in a total of 88,392 participants enrolled in the primary trials. No evidence was found of a protective effect of any combination of antioxidants against breast cancer (RR 1.00, 95 percent CI 0.90-1.09).

The second review¹⁹ examined vitamin E alone or in any combination. It included randomized controlled trials (RCTs) where vitamin E, in tablet or capsule form with or without other components, was evaluated against a control group receiving placebo or no intervention. They assessed the methodological quality of all included trials as high. They identified three trials, involving 62,158 participants, in which breast cancer incidence was reported as an outcome. They concluded that there was no evidence of a protective effect of vitamin E supplementation against breast cancer (RR 0.99, 95 percent CI 0.90-1.10).

Statins. Statins (hepatic 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are a class of lipid-lowering drugs that are widely prescribed for people at risk of cardiovascular disease. Interest in whether use of statins is associated with cancer risk was prompted by safety monitoring findings from cardiovascular prevention trials.⁹¹ Some studies suggest that they may also have a protective effect against cancer,⁹²⁻⁹⁸ while others suggest the opposite.⁹⁹⁻¹⁰¹ Setoguchi et al., (2007)¹⁰² observed that longterm statin users tend to be healthier overall than non-users, and suggested that this might explain the positive associations.

Table 7 summarizes findings from the most comprehensive recent review²⁰ that examined the evidence for statins in reducing the risk of a range of cancers, including breast, colorectal, and prostate (data for the latter two presented below). This review focused on placebo-controlled trials of any statin involving any population except participants being treated for particular high risk indications (e.g., familial hypercholesterolemia). The overall analysis indicated that statins appear to confer neither a protective nor a harmful effect on breast cancer incidence (RR 1.01, 95 percent CI 0.79-1.30). The findings were unaltered in sub-group analyses comparing lipophilic and lipophobic statins, and low, medium, and high potency statins.

Screening. Breast self-examination (BSE). It has been believed for many years that the practice of regular BSE allows women to detect breast tumors at an early stage, and thus to seek early treatment and improve their chances of cure. It is also considered inexpensive, non-invasive, and can be done in private.^{103,104} Observational evidence suggests that women diagnosed with breast cancer who have practiced BSE are more likely to have found the tumor themselves, to have smaller tumors (on average) at the time of diagnosis, and to have benefited from longer survival.¹⁰⁵ Critics of such analyses point to the possibility of lead-time bias, and the need to examine mortality rates as a more valid method of examining outcomes.

We report the findings of one systematic review²¹ which identified primary reports of three large randomized controlled trials, in two of which the intervention was teaching BSE in general populations and, in the third, clinical breast examination followed by teaching BSE. The latter was discontinued after the first screening round because of poor compliance, so data were available for only two trials. A total of 587 breast cancer deaths were observed in a total group of participants of 388,535 across the two trials. The relative risk of breast cancer mortality was 1.05 (95 percent CI 0.90-1.14). There was no statistically significant effect on the total number of cancers identified. There was a non-significant trend towards the detection of smaller tumors (carcinoma in situ RR 1.32, 95 percent CI 0.82-2.14, tumors ≤ 2 cm RR 1.13, 95 percent CI 0.99-1.28). There was a statistically significant increase in total number of breast biopsies and biopsies with benign pathology (RR 1.53, 95 percent CI 1.47-1.60, and 1.88, 95 percent CI 1.77-1.99, respectively). These two large, longterm, population-based trials provide robust evidence that teaching women to perform regular BSE does not translate into a lower mortality rate from breast cancer, and is associated with a higher rate of invasive investigation.

Screening mammography. Mammography as an investigative technology for suspected breast pathology has been available for several decades, and has been gradually introduced, and

evaluated, as a potential screening strategy for breast cancer. The rationale for mammography is that screening may detect tumors at a stage before they are palpable through self- or clinical examination, and that these smaller tumors are less likely to have become locally invasive or metastasized. Screening mammography aims to detect early malignant tumors and, if effective, would be expected to reduce breast cancer, and overall, mortality, but not breast cancer incidence.

Screening mammography has been the focus of a relatively large number of controlled trials in a range of countries, and between 1992 and 2002, 22 systematic reviews of screening mammography were published.¹⁰⁶⁻¹²⁷ This level of scrutiny reflects ongoing controversies about the quality of the primary trials, and the possibility for harm which some experts consider inadequately examined and appreciated.^{106,128}

We summarize the findings of the most recent comprehensive review²² that attempts to address these issues through analyzing the outcome of all-cause mortality as well as breast cancer mortality, by sensitivity analyses according to adequacy of allocation procedures in primary trials, and by assessing rates of different treatment modalities in screened and control groups. The data are presented in Table 7.

This review examined data from 10 completed RCTs involving about half a million women. Of these, the reviewers considered only three trials to have been adequately randomized, and conducted a meta-analysis for these three separately. The trials covered a wide range of age groups, from 39 to 74 years, although most studies focused on women within the 40-59 age group. The reported screening intervals ranged from annual to about 2 years. In some studies, screening was accompanied by clinical breast examination, physical examination, or encouragement to perform monthly BSE. In most trials, the control intervention was usual care.

The overall analysis suggested that screening mammography is associated with reduced breast cancer mortality at 13 years (RR 0.80, 95 percent CI 0.73-0.88), but the association is more marked for the trials considered 'sub-optimally randomized' (RR 0.75, 95 percent CI 0.67-0.83) than for 'adequately randomized trials' (RR 0.93, 95 percent CI 0.80-1.09). When all cause mortality outcomes are considered (which would incorporate serious harms caused by over-treatment), the pooled estimates are very similar for trials considered 'adequately randomized' (RR 1.00, 95 percent CI 0.96-1.04) and 'sub-optimally randomized' (RR 0.99, 95 percent CI 0.97-1.01).

Colorectal Cancer

Six reviews are presented in Table 8 which synthesizes evidence in relation to colorectal cancer (CRC) prevention, four relating to chemoprevention (antioxidants, NSAIDs, and statins) and two relating to screening (FOBT and FS).

Chemoprevention. The rationale for chemoprevention is described in previous section on breast cancer.

Antioxidants. The background to antioxidants is described in previous section on breast cancer.

We report the findings of two reviews which examined antioxidants and CRC incidence. The first¹⁸ evaluated supplements which contained any combination of β -carotene, vitamin C, vitamin E, selenium, zinc, and other antioxidants, and the second¹⁹ focused on vitamin E in any combination. Further details of these reviews are included in the section on breast cancer.

The first review¹⁸ conducted an analysis of 1,523 cancers in a total of 178,086 participants enrolled in the primary trials. No evidence was found of a protective effect of any combination of antioxidants against CRC incidence (RR 1.00, 95 percent CI 0.90-1.10).

The second review¹⁹ identified four trials focusing on CRC. For vitamin E given in any combination (91,099 total participants), they found no evidence of an association with CRC incidence (RR 0.95, 95 percent CI 0.81-1.12). Similarly, there was no association when they examined data from two trials (24,114 participants) which evaluated vitamin E alone (RR 1.05, 95 percent CI 0.79-1.39).

Together, these reviews provide no evidence of a positive or negative association between antioxidant or vitamin E supplementation, and CRC risk.

NSAIDs. NSAIDs are a group of compounds which have an anti-inflammatory effect generally due to their action as non-selective inhibitors of the enzyme cyclooxygenase. Their potential protective effect against CRC has been observed in a number of case-control and cohort studies;¹²⁹⁻¹³⁶ there is also evidence of their effectiveness in preventing recurrence of colorectal adenomatous polyps.^{137,138}

We identified two systematic reviews that examined one specific NSAID only, ASA, in CRC prevention. We report the findings of the single review that conducted a formal meta-analysis.²³ This review identified two primary studies that evaluated CRC incidence (one at 5 years, the other at 10 years) in individuals at average risk (including no personal history of adenomas); one of these trials also reported CRC mortality and the other examined the incidence of colorectal adenomas. The intervention in both of these studies was ASA at doses recommended for cardiovascular protection (i.e., 325 mg every other day or 100 mg/day). Apparently no primary studies of standard doses (i.e., ≥ 325 mg/day) have examined cancer outcomes in average risk individuals. The combined number of participants in these two studies was 61,947. No statistically significant association was identified between low dose ASA and CRC incidence (pooled RR 1.02, 95 percent CI 0.84-1.25), CRC mortality (RR not reported) or adenoma incidence at 5 years (RR 0.86, 95 percent CI 0.68-1.10). These results provide no direct information on the effectiveness of either higher doses of ASA, or other NSAIDs, on colorectal neoplasia.

Statins. The background to statins is described in previous section on breast cancer. A comprehensive systematic review²⁰ examined the evidence for statins in reducing the risk of CRC as well as breast (reported above) and prostate cancer (reported below). Data was synthesized for nine trials which examined CRC incidence, and one which evaluated CRC mortality, as outcomes. The overall analysis indicated that statins appeared to confer neither a protective nor a harmful effect on CRC incidence (pooled RR 1.02, 95 percent CI 0.89-1.16) or mortality (RR 0.33, 95 percent CI 0.07-1.63). The findings were unaltered in sub-group analyses comparing lipophilic and lipophobic statins, and low, medium and high potency statins.

Screening. Evidence from a wide range of studies¹³⁹⁻¹⁴¹ suggests that CRC results from complex interactions between genetic and environmental factors, and that most cancers evolve from small adenomas over a period of years.^{140,141} The possibility of preventing CRC cases and deaths by early intervention to remove colorectal adenomas and/or early stage cancers has led to a large number of studies of a range of screening strategies, specifically involving FOBT, colonoscopy and sigmoidoscopy.¹⁴² There is no consensus on the optimum combination of these modalities, or on the ideal screening interval.

FOBT. The most widely used approach to FOBT is the stool guaiac test, in which the presence of heme (from haemoglobin) is indicated by a color change when hydrogen peroxide is

added. This is a result of the oxidation of guaiac by the peroxide. A newer class of occult blood tests (immunochemical) rely on the detection of globin rather than heme, and it is suggested that these are more sensitive and specific than guaiac tests.¹⁴³

A number of reviews examined FOBT-based screening strategies, of which one is reported here.²⁴ This review examined RCTs only of FOBT (guaiac or immunochemical) in which at least two rounds of screening were compared with no-screening controls. This review analyzed data from four trials involving a total of 329,642 participants. A statistically significant effect of screening on CRC mortality was observed (pooled RR 0.84, 95 percent CI 0.78-0.90), which remained when the three trials with biennial screening were examined separately. No effect on all-cause mortality was observed (pooled RR 1.00, 95 percent CI 0.99-1.01), but a statistically borderline association with non-CRC mortality was noted (pooled RR 1.01, 95 percent CI 1.00-1.03). The interpretation of these combined results is difficult. It is argued that effective CRC screening would have little impact on all-cause mortality because CRC makes only a small contribution to overall mortality in these populations (and screening trials are therefore inadequately powered to detect such an effect). There is also an argument that biased attribution of cause of death between screened and control groups can lead to an overestimate of the true effect of screening on mortality, therefore an assessment of all-cause mortality would provide a more valid assessment of effectiveness.¹⁴⁴

We do not present data from a further systematic review³⁶ which focused on guaiac-based biennial FOBT screening alone; it included a non-randomized controlled trial excluded from the review reported above²⁴ and excluded one of the latter's included trials. The pooled results are consistent with those reported above and in Table 8.

Flexible sigmoidoscopy. Flexible sigmoidoscopy (FS) is an endoscopic technique which allows visualization of the colon and rectum distal to the splenic flexure. FS has a very low complication rate.^{145,146} The majority of CRCs arise in the distal colon, thus are theoretically detectable with FS, and detection of distal adenomas is an indication for full colonoscopy.¹⁴⁷ It is suggested that a combined strategy such as this can detect about 80 percent of CRC cases in men and about 50 percent of those in women, without recourse to more invasive colonoscopy as a primary screening modality.¹⁴⁸⁻¹⁵⁰

We identified one review²⁵ which examined the evidence for FS in CRC screening. One RCT was identified which compared FS in addition to FOBT against FOBT only (positive screens being followed up by colonoscopy). This review also considered FOBT alone as a screening strategy, but the data were not extracted as they are similar to the review reported above.²⁴ This trial involved 10,978 participants and showed no statistically significant effect of the combined FS plus FOBT strategy on CRC mortality or incidence (RR 0.78, 95 percent CI 0.36-1.73 and 1.37, 95 percent CI 0.88-2.15, respectively). No formal intervention studies comparing FS alone with either no screening, or FOBT only, have been identified.

Prostate Cancer

Five reviews^{18-20,26,27} are presented in Table 9 which synthesizes evidence in relation to prostate cancer prevention, four relating to chemoprevention (antioxidants, calcium, and statins) and one relating to screening (PSA, digital rectal examination (DRE), and transurethral ultrasound (TRUS) biopsy).

Chemoprevention. The rationale for chemoprevention is described in previous section on breast cancer.

Antioxidants. The background to antioxidants is described in previous section on breast cancer.

We report the findings of two reviews which examined antioxidants and prostate cancer incidence. The first¹⁸ evaluated supplements which contained any combination of β -carotene, vitamin C, vitamin E, selenium, zinc, and other antioxidants, and the second¹⁹ focused on vitamin E in any combination. Further details of these reviews are included in the section on breast cancer.

The first review¹⁸ conducted an analysis of 2,143 new cancers in a total of 55,709 participants enrolled in the primary trials. Overall, the pooled analysis indicated a small, non-statistically significant decrease in prostate cancer incidence when all antioxidants were considered together (pooled RR 0.87, 95 percent CI 0.74-1.02). Noting high heterogeneity, a sensitivity analysis suggested that vitamin E in particular was associated with a reduced risk (pooled RR 0.82, 95 percent CI 0.67-0.99), based on three trials. The authors of this review also noted that “one trial report a decreased incidence of prostate cancer with selenium,” although they did not provide relative risk data. Reporting on the same trial,¹⁵¹ another review²⁶ (included below) estimated that, for a daily dose of 200 μ g of selenium (compared with placebo), the relative risk for prostate cancer incidence was 0.37 (95 percent CI 0.20-0.70).

The second review¹⁹ evaluated the effect of vitamin E alone or in combination, and performed a meta-analysis on three primary trials. For vitamin E given in any combination (71,759 total participants), the pooled estimate for effect on prostate cancer incidence also indicated slightly reduced risk (pooled RR 0.85, 95 percent CI 0.74-0.96). Two trials examined vitamin E alone, with no evidence of an association (pooled RR 0.86, 95 percent CI 0.70, 1.06). Similarly, there was no association when they examined data from two trials (24,114 participants) which evaluated vitamin E alone (RR 1.05, 95 percent CI 0.79-1.39).

Together, these reviews suggest no evidence of an effect of combined antioxidant supplementation on prostate cancer risk, but potentially a small protective effect of vitamin E supplementation.

Calcium. The association between calcium intake and prostate cancer risk has been examined both from risk increasing and risk reducing perspectives. Observational studies have indicated a positive association between calcium intake and prostate cancer, the suggested mechanism being that calcium lowers circulating vitamin D concentrations, and this in turn alters prostate cell proliferation.¹⁵²⁻¹⁵⁵ In contrast, some studies have suggested that dietary calcium decreases prostate cancer risk.¹⁵⁶⁻¹⁶²

We identified one review which analyzed intervention study data relating to calcium and prostate cancer risk.²⁶ This review identified a single primary trial of calcium supplementation, designed to evaluate calcium as a protective agent against recurrence of colorectal adenomas, where prostate cancer incidence was evaluated as a secondary outcome.⁴⁷ Supplements equivalent to 1,200 mg elemental calcium daily were given for 4 years and participants followed up for another 7 years. This trial observed 70 prostate cancers in 672 men with an RR for prostate cancer incidence of 0.83 (95 percent CI 0.52-1.32). Detailed review of the results suggested a statistically significantly lower incidence of prostate cancer in the supplement group until 2 years after supplementation was discontinued (RR 0.52, 95 percent CI 0.28-0.98), at which point the risk in both groups converged. It is suggested that calcium may have a slight protective effect, which is maintained only by ongoing supplementation. This finding from a single trial is insufficient to recommend calcium supplementation specifically for the purpose of

prostate cancer prevention, particularly given the contradictory findings of previous observational studies.

Statins. The background to statins is described above in previous section on breast cancer.

We present data from the comprehensive systematic review described in previous sections,²⁰ which examined the effectiveness of statins in reducing the risk of several cancers. Four trials examined prostate cancer incidence, and one evaluated prostate cancer mortality. The overall analysis indicated that statins appeared to neither increase nor decrease risk of prostate cancer incidence or mortality (pooled RR 1.00, 95 percent CI 0.85-1.17 and RR 0.99, 95 percent CI 0.14-7.01 respectively). No data were presented with regard to lipophilic versus lipophobic, or low, medium and high potency statins.

Screening. *Prostate-specific antigen-based strategies (PSA).* Strategies for screening for early prostate cancer have revolved around the combined use of PSA with or without DRE of the prostate, followed by needle biopsy guided transrectal ultrasound (TRUS). Digital rectal examination has limited sensitivity because it is not possible to palpate the entire prostate gland, while PSA testing produces high rates of false positive and false negative results.¹⁶³ In addition, although reductions in prostate cancer mortality have been demonstrated with early treatment,^{164,165} there remains considerable concern about lead and length time bias, the overtreatment of men who have indolent disease (tumors which were never destined to be fatal),¹⁶⁶ and harms associated with treatment.¹⁶⁷⁻¹⁷⁰

We identified a single review²⁷ which examined the effectiveness of population-based screening in preventing death from prostate cancer. This study identified two trials of screening strategies that combined PSA testing, DRE and TRUS biopsy for diagnostic investigation, one of which used an annual, the other a 3 times yearly, screening cycle. The total number of participants randomized was 55,512, and 345 prostate cancer deaths were observed over followup periods of at least 11 years. No statistically significant impact of screening on prostate cancer mortality was found (pooled RR 1.01, 95 percent CI 0.80-1.29). No data were presented in relation to all-cause mortality. The authors of the review considered that both trials had a high risk of bias. The overall findings indicate that PSA-based screening cannot be considered to be an effective secondary prevention intervention in prostate cancer.

Quality Assessment of Studies

Standardized quality assessment checklists using a modified scoring version of the Oxman and Guyatt criteria⁸² were employed for all systematic reviews. The range of scores was 11-17 out of a possible 18. The major area of weakness was failure to describe adequate control of bias in the selection of studies for review.^{18-20,22,23,27} Other issues encountered in a minority of reviews were incomplete description of search methods,^{23,27} and failure to describe criteria for assessing the validity of primary studies,^{20,25,26} or to cite the validity assessments of included studies.^{20,26}

Overall, the potential for bias in these reviews appears quite low. It is impossible to say whether failing to adequately describe search strategies, methods for controlling selection bias, or assessing validity of studies reflects methodological shortcomings or only failure to report these in published articles.

Conclusion

We were able to locate relevant systematic reviews relating to prevention, in average risk populations, of breast, colorectal, and prostate cancers, but not ovarian cancer. For all three cancers, the core primary prevention strategy for which reviews could be identified was chemoprevention. For breast and CRC, no evidence of an effect on cancer incidence of antioxidant supplements in general, vitamin E supplements in particular, or statins. For CRC, data on NSAIDS were available, with no evidence of an effect on cancer incidence. For prostate cancer, equivocal evidence was found of a possible protective effect of vitamin E supplements, selenium, and calcium supplements.

Screening strategies were also examined. For breast cancer, a review of three large population-based trials, confirm that BSE is not an effective strategy for reducing mortality from breast cancer and may increase morbidity through unnecessary investigations. Screening mammography has been evaluated in a large number of meta-analyses, which indicate that population-based screening appears to consistently reduce breast cancer mortality by about 15 percent, although there is still an open debate on whether all-cause mortality is a more valid measure of benefit of this intervention. There is concern that screening leads to higher rates of investigation and over treatment which undermine overall benefits. The analyses are based on studies with participants with a wide range of age ranges, which makes it difficult to discern the extent to which the profile of benefits and risks change according to target age. Both the technical performance of the screening test, in terms of sensitivity and specificity, and the prior risk of breast cancer, vary according to age, therefore the predictive value is not constant across all age groups. Also, the level of any risks associated with overtreatment will depend on local protocols for diagnostic investigation and treatment.

For CRC, FOBT-based screening strategies (which generally include diagnostic investigation using colonoscopy) appear to be associated with a decrease in CRC mortality, and the limited evidence available suggests that adding FS does not improve their effectiveness. As with breast screening, it is argued that all-cause mortality may provide a more valid assessment of screening effectiveness; however, since the proportion of overall mortality attributable to CRC is low, screening studies are generally underpowered to detect an effect.

With respect to prostate cancer, we found no evidence that PSA-based screening strategies are effective in reducing mortality.

Research Q3: For Those Interventions Identified as Being Based on Reasonable Evidence, What is the Evidence That Providing Information on Risk Status Results in Behavior Change or Increased Uptake of Services on the Part of Individual Patients?

General Approach

We reviewed published intervention studies (RCTs, controlled trials, and before-after studies) that examined the impact of systematic collection of family history information on one or more risk-reduction behaviors for breast, ovarian, colorectal, or prostate cancer. To be

included, the intervention had to comprise systematic collection of individual family history information, and also communication of personal risk of one or more of the cancers of interest. This could be accompanied by individualized advice on specific risk reduction behaviors, although this was not necessary for a study to be included. The target behaviors of interest were both personal/lifestyle, and adherence to recommended clinical preventive interventions such as screening; the interventions were those considered standard of care when the primary study was conducted.

Studies Reviewed

Three studies⁴⁸⁻⁵⁰ were retained for data abstraction after full text review. These studies all focused on breast cancer risk assessment and mammography screening, with or without other behaviors, as the target intervention (Table 10). Two of the studies were RCTs^{49,50} and the other⁴⁸ was an uncontrolled before-after study.

The sample sizes ranged from 188 to 2,076, and participants were recruited from a health maintenance organization (HMO),⁴⁹ community pharmacies/health promotion events,⁴⁸ and as first degree relatives (1DR) of breast cancer patients.⁵⁰ Family history information was captured by computer-assisted telephone interview,⁵⁰ postal questionnaire,⁴⁹ and interviewer-administered questionnaire.⁴⁸ In all three studies, information relating to personal medical history was collected as well as family history information. The 1DR and community pharmacy studies^{48,50} specified use of the Gail model for risk calculation, which requires information on the number of 1DRs with breast cancer; the HMO study⁴⁹ used a risk stratification algorithm developed in-house, which included information on first and second degree relatives with breast cancer.¹⁷¹

The HMO study⁴⁹ had four groups, with two levels of collection of family history information (collected or not collected) and three levels of risk information included in screening invitation letters (no reinforcement, general risk messages, personalized risk messages) in the following combinations:

- no collection of individual risk information plus generic invitation for mammography
- no collection of individual risk information plus general risk messages embedded in invitation for mammography
- collection of individual risk information plus general risk messages embedded in invitation for mammography
- collection of individual risk information plus personalized risk messages embedded in invitation for mammography.

Data on the outcome of mammography uptake by 12 months were captured using the HMO's databases.

The 1DR study⁵⁰ had two groups, both of which had individual family history information collected, and personalized information on risk of breast cancer fed back. The two groups had different levels of reinforcement of the importance of, and reminders to undertake, the target behavior of screening mammography. Data on the outcome of uptake of mammography was assessed by self-report at 12 months, captured by mail or telephone survey.

The community pharmacy study⁴⁸ had one group of participants, all of whom had individual family history information collected and personalized information on risk of breast cancer fed back, along with reminders of recommended screening behaviors. Data on the outcomes of self-reported uptake of mammography, and adherence to BSE and clinical breast examination (CBE) recommendations, was captured at 6 months using telephone survey.

It should be noted that the two controlled studies (1DR and HMO^{49,50}) both examined different levels of personalization of risk information, but only the HMO study⁴⁹ examined the capture of family history information as an intervention in itself. The community pharmacy study⁴⁸ did not have a control group without family history capture.

Outcomes

The findings of the evaluation studies of the interventions described above are summarized in Table 11. The 1DR study⁵⁰ showed a borderline statistically significant difference ($P=0.05$) in the change in mammography uptake (about 8 percent) between intervention and control groups. The other two studies were null. The community pharmacy study⁴⁸ was the only one to examine other behaviors, and showed a statistically significant increase in self-reported BSE, but not CBE. The HMO study appeared to be adequately statistically powered; this was also likely the case with the 1DR study although sample size considerations were not discussed. Although the community pharmacy study indicated an *a priori* sample size calculation, their assumptions about baseline adherence rates may have been erroneous, as they were around 70-80 percent for CBE and mammography, much higher than published general population figures and suggestive of a possible ceiling effect.

All articles reported age-specific analyses, which generally did not show meaningful differences in effectiveness of the interventions. The HMO study⁴⁹ also analyzed outcomes by breast cancer family history status (positive or negative) in the two groups that had been sent a risk questionnaire. While mammography uptake was similar between those receiving general risk and personalized risk invitations and who had a negative family history (41.4 and 39.7 percent, respectively), uptake was higher in women who had a positive family history and received a personalized invitation (66.7 percent) than women with a positive family history who received a generalized risk invitation (42.9 percent) ($P=0.005$). The results of the community pharmacy study⁴⁸ were unchanged when the analyses were limited to the high risk participants only.

The studies vary in the extent to which their participants were representative of the general population. The HMO study was designed to be completely representative of its own patient population, which was described in previous publication as predominantly white, slightly better educated, and having a slightly different income distribution than Washington state as a whole.¹⁷¹ The proportion of participants with a positive first or second degree family history of breast cancer was about 20 percent, which is consistent with the North American female population. In contrast, the 1DR study was confined to women who had at least one first degree relative with breast cancer. The community pharmacy study drew participants from women attending pharmacies and heart health events, and no specific data are presented regarding representativeness. Their analyses indicate that 21 of 140 (15 percent) participants were assigned to the high risk category (≥ 1.7 percent risk of breast cancer in 5 years), which appears higher than would be expected for an unselected female population in this age group. Also, the high baseline rates of CBE and mammography compared with published figures for the general population may indicate that this study has limited external validity.

Quality Assessment of Studies

Standardized quality assessment checklists were employed on the two studies that used a randomized trial design.^{49,50} The modified Jadad scores were 4 out of 8 for both studies.⁸³ The

main problem areas for both studies were failure to report measures to achieve blinding, and neither explicitly described randomization procedures or measures to conceal allocation. Both studies implemented the intervention through mail-outs to participants, asking them to take a specific action (schedule a mammography), and the possibility for contamination was probably rather low, particularly for the 1DR study. The potential for bias in these studies therefore appears quite low.

The third study⁴⁸ was described in the report's abstract as a 'randomized, paired, pre-post study', which is misleading. In our assessment, it was an uncontrolled pre-post study in which before-after outcomes for individual participants were analyzed as paired data. No control group was used and therefore no random allocation was possible. The potential for bias in this study is high, given that no assessment could be made of the influence of external factors, or placebo or Hawthorne effects.

Conclusion

Taken together, the three studies identified neither support nor refute the hypothesis that taking family history and using it to personalize risk of breast, ovarian, colorectal, or prostate cancer promotes lifestyle changes which reduce cancer risk, and/or greater adherence with preventive clinical interventions. All three studies focused on breast cancer, the interventions were heterogeneous, some including components beyond family history taking and personalization of risk. The interventions generally did not resemble the routine, personal interaction which might occur between a primary care professional and an individual patient, and the methodological rigor of the evaluations was variable.

The HMO study⁴⁹ was embedded in a routine screening invitation system, and therefore resembled regular clinical practice, albeit in a non-personal way. The evaluation was well-designed and had a large sample size. This study (the oldest of the three reviewed) provides no evidence that personalization of risk information would be an effective overall strategy, but suggests that it might be worth exploring as a way of promoting risk reduction behavior in high risk sub-groups.

The 1DR study⁵⁰ provided evidence of a possible modest effect on mammography uptake of personalizing risk information for a group already likely to have higher than average personal risk perceptions. The intervention had several components, and it is impossible to separate out the individual effects of the family history collection, the personalization of risk information, and the materials designed to reinforce the importance of mammography. Even this thoughtfully designed intervention produced only a small increase in screening behavior. The transferability of the approach to a clinical setting, and the absolute size of benefits that would be achieved, is unclear.

The community pharmacy study⁴⁸ showed some evidence that personalized risk information could promote cancer prevention behavior, but the lack of a control group, the questionable validity of the outcome measurement, and the likely selection bias of participants all make it impossible to judge the wider applicability of its findings.

Research Q4: What are the Harms or Risks to Individual Patients That may Result From the Collection of Family History Information in Itself, and/or the Provision of Family History-Based Risk Information?

General Approach

We reviewed published intervention studies, (RCTs, controlled trials, and before-after studies) which assessed negative impacts of systematically collecting family history information and providing patients with risk information for the cancers of interest based on their family history. The focus was on systematic collection of individual family history information, and communication of personal risk of one or more of the cancers of interest, in populations considered representative of primary care populations. Specialist genetic counseling (with or without genetic testing) for patients selected because of possible genetic risk was excluded from this definition.

The outcomes of interest were impaired quality of life, negative psychological effects (cognitive, affective, or behavioral), social impacts (e.g., negative impact on family well-being, discrimination, stigmatization), which could be directly attributed to this intervention, not subsequent clinical or other preventive activities.

Studies Reviewed

One study was identified which met all eligibility criteria.⁵¹ This was an uncontrolled before-after study designed to evaluate the psychological impact of providing family history information and receiving a personalized risk assessment. Patients aged 35-65 registered with a single family doctor's office were invited to complete a postal cancer family history questionnaire, and were provided with individual feedback on their genetic risk of CRC and breast cancer (where appropriate). General anxiety and cancer worry was assessed at baseline and 4 to 6 weeks after risk information feedback using the Spielberger State-Trait Inventory (STAI) and a multidimensional cancer worry scale, respectively. Details of the study are summarized in Table 12.

Outcomes

This study analyzed participants in two groups. Firstly, 'lower risk' (those at no more than slightly elevated risk) participants, for whom no followup was necessary, were given feedback by letter only. No statistical difference was observed in anxiety and most other cancer worry measures following the intervention, with the exception of a small reduction in participants' perception of their own risk ($P < 0.01$).

Of the remaining participants, most were interviewed to clarify details of the family history, which led to further designation into 'higher risk' and 'false positive' groups (the latter comprising patients deemed not actually to be at high risk after further enquiry). For both 'higher risk' and 'false positive' groups, no difference between baseline and followup responses to general anxiety and cancer worries scales was observed. However, both of these groups showed

higher baseline cancer risk perception scores compared to the lower risk group ($P < 0.001$ for 'higher risk' group and $P = 0.003$ for 'false positive' group).

Overall, the findings suggested no association between the exercise of capturing family history information and feeding back personalized risk, and anxiety or cancer worry, in patients who are close to average risk. In fact, it is possible that the intervention may have led to more realistic (lower) perceptions of personal risk. In contrast, the higher anxiety and cancer worry outcomes in the 'true' and 'false positive' high risk groups may reflect their baseline (pre-intervention) status rather than an effect of family history taking.

Conclusion

The evidence base for addressing (Q4) is limited to a single study. It suggested that structured family history collection and feedback of breast cancer risk information had no deleterious psychological effects on any of the risk groups, and in women, who were not at high risk, may have led to appropriate reductions in perceived risk. Higher average baseline levels of anxiety and cancer worry in the groups who went on to have further assessment may reflect pre-existing concerns about a positive family history and need to be taken into account when family history interventions are evaluated.

Table 4. Details of risk prediction models

System	Cancer	Family history items	Other items	Output	Relevant studies	Comments
Gail model (GM) ¹⁵	Breast	1DRs with BC Age at first birth <20y (0, 1, ≥2) 20-24y (0, 1, ≥2) 25-29 y or nulliparous (0, 1, ≥2) ≥30y (0, 1, ≥2)	Age Ethnicity Age at menarche Age at first live birth # previous breast biopsies (0, 1, >1) Presence of atypical hyperplasia on biopsy	Risk of BC	Adams-Campbell ¹⁰ (2007) Spiegelman ⁸ (1994)	Assumes annual screening Cancer incidence rates derived from BCDDP ¹⁵
Modified GM (MGM) ⁸⁴	Breast	As for GM	As for GM	Risk of invasive BC	Chlebowski ¹³ (2007) Adams-Campbell ¹⁰ (2007) Rockhill ⁹ (2001) Boyle ¹¹ (2004) Decarli ¹² (2006)	Assumes annual screening Cancer incidence rates derived from SEER data
MGM for black/African Americans (GM-B) ¹⁰	Breast	As for GM	As for MGM	As for MGM	Adams-Campbell ¹⁰ (2007)	MGM revised using age-specific invasive rates and specific attributable risk estimates for African-American women

Abbreviations: 1DR=first degree relative; AUC=area under the curve; BC=Breast cancer; BCDDP=Breast Cancer Detection Demonstration Project; CI=confidence interval; CRC=Colorectal cancer; E=Expected events; GM=Gail Model; GM-B=GM for blacks/African Americans; IT-GM=GM for Italian population; MGM=Modified GM; O=Observed events; NHS= National Health Service; RCT=Randomized controlled trial; RR=Relative risk; SEER=Surveillance, Epidemiology and End Results; y=years;

Table 4. Details of risk prediction models (continued)						
System	Cancer	Family history items	Other items	Output	Relevant studies	Comments
MGM for Italian population (IT-GM) ^{11,12}	Breast	As for GM	As for MGM, except # previous breast biopsies replaced by any breast biopsy (no, yes)	As for MGM	Boyle ¹¹ (2004) Decarli ¹² (2006)	MGM revised using age-specific invasive rates and specific attributable risk estimates for Italian women
CARE model for African American population ⁷	Breast	Number of affected relatives (mother, sisters)	Age Age at menarche # previous breast biopsies, (<50y, ≥50y) Presence of atypical hyperplasia on biopsy (Age at first live birth)	As for MGM	Gail ⁷ 2007	MGM re-developed for African American populations using age-specific invasive rates and specific attributable risk estimates from control data from the CARE Study and SEER program.
Harvard Cancer Risk Index ¹⁶	Colon	Brother/sister/parent with colon cancer	Red meat intake Vegetable intake Alcohol intake Multivitamin use Physical activity Body mass index Height Colonoscopy/sigmoidoscopy screening (Aspirin use)	10 year cancer risk	Kim ¹⁴ 2004	Designed to assess risk of multiple cancers Validation using family history data published only for colon cancer

Table 5. Evaluations of risk prediction models

Study Design	Tool(s)	Participants	Outcome measure(s), timing ascertainment	Algorithm performance	Conclusions
Spiegelman ⁹ 1994	GM	n=115,172	12 y BC incidence	Calibration O, E E/O (95% CI) O=2,396, E=3,196 E/O=1.33 (1.28-1.39) Discrimination Correlation coefficient (Pearson) 0.67 (Spearman) 0.04	Significant overestimation of overall BC risk Modest discriminatory accuracy
Rockhill ⁹ 2001	MGM	n=82,109	5 y BC risk	Calibration O, E E/O (95% CI) O=1,354, E=1,273.42 E/O=0.94 (0.89-0.99) Discrimination AUC (95% CI) 0.58 (0.56-0.60) RR=(95% CI) 2.83 (2.19-3.65) Sensitivity, specificity (cut point=1.67% 5 y risk): Se=0.44, Sp=0.66	Fairly well calibrated model Modest discriminatory accuracy

Abbreviations: 1DR=first degree relative; AUC=area under the curve; BC=Breast cancer; CI=confidence interval; CRC=Colorectal cancer; E=Expected events; GM=Gail Model; GM-B=GM for blacks/African Americans; IT-GM=GM for Italian population; MGM=Modified GM; O=Observed events; NHS= National Health Service; RCT=Randomized controlled trial; RR=Relative risk; Se=sensitivity; SEER=Surveillance, Epidemiology and End Results; Sp=specificity; y=years;

¹Performance by other cut-off points also reported

Table 5. Evaluations of risk prediction models (continued)

Study Design	Tool(s)	Participants	Outcome measure(s), timing ascertainment	Algorithm performance	Conclusions
Chlebowski ¹³ 2007	MGM	n=147,916 Mean age 63 y (range 50-79 y) "Ethnically diverse" Excluded: History of BC, mastectomy Suspicious baseline mammogram <5 y followup	5 y invasive BC risk, assessed by annual or semi-annual ascertainment by mail or telephone questionnaire Cancer verified through pathology reports	Calibration O, E E/O O=3,236, E=2,562 E/O=0.79 (p<0.001) Discrimination AUC (95% CI) 0.58 (0.56-0.60)	Poorly calibrated, underestimated number of invasive BCs in 5 years by about 20% Modest discriminatory accuracy
Adams-Campbell ¹⁰ 2007	MGM GM-B	n=1,450 Age: 21-69 y Enrolled 1995 Diagnosed with BC 1995-2003, aged ≥35 y (cases) Age-matched, no BC by 2003	5 y invasive BC risk, assessed by biennial questionnaires	Discrimination Sensitivity, specificity (cut point=1.7% 5 y risk) MGM Se=0.18, Sp=0.86 MGM-B Se=0.04, Sp= 0.97	The MGM and MGM-B perform poorly at predicting risk of invasive BC in African American women Limited discriminatory accuracy

Table 5. Evaluations of risk prediction models (continued)

Study Design	Tool(s)	Participants	Outcome measure(s), timing ascertainment	Algorithm performance	Conclusions
Boyle ¹¹ 2004 Secondary analysis of RCT data ¹⁷²	IT-GM MGM	n=5,383 Women had hysterectomies and no benign breast disease	5 y BC incidence	<p>Calibration O, E E/O (95% CI)</p> <p>IT-GM O=79, E=82.5 E/O=0.92 (0.68-1.16)</p> <p>MGM O=79, E=88.4 E/O=0.86 (0.64-1.08)</p> <p>Discrimination AUC</p> <p>IT-GM 0.58</p>	<p>Reasonably well calibrated</p> <p>Modest discriminatory accuracy in the population studied</p> <p>Data were missing on atypical hyperplasia on biopsies</p>

Table 5. Evaluations of risk prediction models (continued)

Study Design	Tool(s)	Participants	Outcome measure(s), timing ascertainment	Algorithm performance	Conclusions
Decarli ¹² 2006	IT-GM MGM	n=10,031 Age: 35-64	5 y invasive BC risk Method of ascertainment not reported in this paper.	<p>Calibration O, E E/O (95% CI)</p> <p>IT-GM O=194, E=186.11 E/O=0.96 (0.84-1.11)</p> <p>MGM O=194, E=180.1 E/O=0.93 (0.81-1.08)</p> <p>Discrimination Average age-specific AUC (95% CI)</p> <p>IT-GM 0.59 (0.54-0.63)</p> <p>MGM 0.58 (0.55-0.63)</p>	MGM and IT-GM both well calibrated Modest discriminatory accuracy in the population studied
Gail ⁷ 2007	CARE	n=14,059 Age: ≥50	5 y age-specific invasive BC risk	<p>Calibration O/E ratio (95% CI): 1.08 (0.97-1.20)</p> <p>Discrimination Unweighted average age-specific AUC (95% CI): 0.555 (0.535-0.575)</p>	Good calibration, very modest discriminatory accuracy.

Table 5. Evaluations of risk prediction models (continued)

Study Design	Tool(s)	Participants	Outcome measure(s), timing ascertainment	Algorithm performance	Conclusions
Kim ¹⁴ 2004	HCRI	n=52,668 Females Age: median 52	10 y colon cancer incidence	<p>Calibration O/E(95% CI)</p> <p>Overall O/E not reported</p> <p>By HCRI category:</p> <p>2.10≤RR≤5.10 1.79 (0.89-2.70)</p> <p>1.10≤RR≤2.10 1.39 (1.12-1.67)</p> <p>0.90≤RR≤1.10 1.00 (0.66-1.34)</p> <p>0.50≤RR≤0.90 0.89 (0.68-1.09)</p> <p>0.20≤RR≤0.50 0.58 (0.37-0.79)</p> <p>Discrimination AUC (95% CI): 0.67 (0.64-0.70)</p>	Good calibration, moderate discriminatory power

Table 5. Evaluations of risk prediction models (continued)

Study Design	Tool(s)	Participants	Outcome measure(s), timing ascertainment	Algorithm performance	Conclusions
Kim ¹⁴ 2004	HCRI	n=38,953 Males Age: median 51	10 y colon cancer incidence	<p>Calibration O/E(95% CI)</p> <p>Overall O/E not reported</p> <p>By HCRI category:</p> <p>2.10≤RR≤5.10 2.35 (1.12-3.59)</p> <p>1.10≤RR≤2.10 1.34 (1.02-1.66)</p> <p>0.90≤RR≤1.10 1.01 (0.64-1.39)</p> <p>0.50≤RR≤0.90 0.75 (0.56-0.95)</p> <p>0.20≤RR≤0.50 0.83 (0.60-1.07)</p> <p>Discrimination AUC (95% CI): 0.71 (0.68-0.74)</p>	Poor calibration (possibly due to potential misclassification – older cohort at baseline), moderate discrimination

Table 6. Target interventions for review

Cancer	Intervention
Breast	Chemoprevention Breast self-examination Clinical breast examination Screening mammography Screening MRI
Ovarian	Screening ultrasound
Colorectal	Chemoprevention FOBT screening Screening colonoscopy Screening sigmoidoscopy
Prostate	Chemoprevention PSA screening Digital rectal examination
All	Regular exercise/physical activity Dietary interventions - high fiber diet - high fruit and vegetables - low fat Vitamin and micronutrient supplementation Limitation of alcohol intake Smoking cessation Seeking health care advice Referral for genetic counseling and/or genetic testing, where criteria are met

Abbreviations: FOBT=fecal occult blood test; MRI=magnetic resonance imaging; PSA=prostate specific antigen

Table 7. Breast cancer preventive interventions

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Followup duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Type of intervention: Chemoprevention (antioxidants, NSAIDs, and statins)										
Bardia ¹⁸ 2008	Antioxidant supplementation: β-carotene Selenium Zinc Vitamin C Vitamin E or any others	Quant	People at average risk of cancer	RCTs; Supplements with fully disclosed components and not dietary increases in nutrients; placebo-controlled; ≥1 y of followup; reported overall cancer incidence	≤12 (n not reported for cancer-specific analyses)	NR	88,392 (total across all trials)	NR	BC incidence (any antioxidant) RR=1.00 (0.90-1.09)	No evidence of protective effect of antioxidants against risk of BC

Abbreviations: BC=breast cancer; BSE=breast self-examination; DRE=digital rectal exam; e.g.=example; FOBT=fecal occult blood test; HP=High potency; LI=Lipophilic; LO=Lipophobic; LP=Low potency; mg=milligrams; MP=Medium potency; NR=not reported; PHS=Physician's Health Study; PSA=prostate specific antigen; Qual=Qualitative; Quant=Quantitative; RCT=Randomized controlled trial; RR=Relative risk; SM=Screening mammography; SR=systematic review; TRUS=transrectal ultrasound; y=year; WHS=Women's Health Study

Table 7. Breast cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Followup duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Alkhenizan ¹⁹ 2007	Vitamin E alone Vitamin E as part of other supplements	Quant	≥18 y; range of pre-existing health states, but not high risk for BC	RCTs; Supplementation in capsule or tablet form; control = placebo or no intervention; reported total mortality, cancer mortality, cancer-specific mortality	3	≥510 days - ≤10 y (not reported separately for individual cancers)	62,158 (total across all studies)	NR	BC incidence (Vit E in any combination) RR=0.99 (0.90-1.10)	No evidence of protective effect of Vitamin E against BC
Browning ²⁰ 2006	Statins	Quant	All populations except highly specific statin-using patients (e.g. familial hypercholesterolemia, renal transplant)	RCTs; Control = placebo; Reported all cancer, site-specific cancer incidence or mortality	1-7 (depending on analysis)	Median followup: Trials: 3.6 y Observational studies: 6.2 y	RCTs: n = 103,573 Observational studies: n = 826,854	RCTs: 18-82 y Observational studies: 30-89 y	BC incidence from use of statins: 1. All studies RR=1.01 (0.79-1.30) 2. LI (3 trials) RR=0.89 (0.62-1.27) 3. LO (4 trials) RR=1.15 (0.81-1.64) 4. LP (1 trial) RR=1.44 (0.62-3.37) 5) MP (4 trials) RR=1.15 (0.81-1.64)	No evidence of protective effect

Table 7. Breast cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Followup duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
									6) HP (2 trials) RR=0.80 (0.54-1.19)	
Type of intervention: Screening										
Kosters ²¹ 2003	BSE	Quant	General population	RCTs	3 trials, 1 discontinued China Russia	10-12	122,471- 266,064	30-74	1. BC mortality (longest available followup) RR=1.05 (0.90-1.14)	The trials are based on large sample sizes and the findings are robust. Uptake was high and the findings are applicable to BSE practice generally. There is no effect of BSE on breast cancer mortality, but evidence that women taught BSE were more likely to be referred for a biopsy.

Table 7. Breast cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Followup duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Gøtzsche ²² 2006	SM	Quant	Women without previously diagnosed BC	RCTs; Controls with no SM	3 'adequately randomized' trials Canada 7 'suboptimally randomized' trials	7-13	42,482-92,934	39-74	<p>All trials BC mortality (13 y): RR=0.80 (0.73-0.88)</p> <p><i>Suboptimally randomized' trials</i> RR=0.75 (0.67-0.83)</p> <p><i>Adequately randomized' trials</i> RR=0.93 (0.80-1.09)</p> <p>All cause mortality RR=1.00 (0.96-1.04)</p> <p><i>Suboptimally randomized' trials</i> RR=0.99 (0.97-1.01)</p> <p>All cancer mortality RR=1.02 (0.95-1.10)</p>	Screening likely reduced BC mortality, with a reasonable risk reduction estimate of about 15%. Screening also leads to over diagnosis and over treatment. "It is not clear whether screening does more good than harm"

Table 8. Colorectal cancer preventive interventions

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Followup duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Type of intervention: Chemoprevention (antioxidants, NSAIDs, and statins)										
Bardia ¹⁸ 2008	Antioxidant supplementation: β-carotene Selenium Zinc Vitamin C Vitamin E or any others	Quant	People at average risk of cancer	RCTs; Supplements with fully disclosed components and not dietary increases in nutrients; placebo-controlled; ≥1 y of followup; reported overall cancer incidence	≤12	NR	178,086 (total across all studies)	NR	CRC incidence (any antioxidant) RR=1.00 (0.90-1.10)	No evidence of protective effect of antioxidants against CRC

Abbreviations: ASA=acetylsalicylic acid; BC=breast cancer; BSE=breast self-examination; DRE=digital rectal exam; e.g.=example; FOBT=fecal occult blood test; HP=High potency; LI=Lipophilic; LO=Lipophobic; LP=Low potency; mg=milligrams; MP=Medium potency; NR=not reported; PHS=Physician's Health Study; PSA=prostate specific antigen; Qual=Qualitative; Quant=Quantitative; RCT=Randomized controlled trial; RR=Relative risk; SR=systematic review; TRUS=transrectal ultrasound; y=year; WHS=Women's Health Study
 * Kerr review also examines FOBT screening alone, but results overlap, and are consistent, with those of Hewitson & Heresbach, therefore not reported here.

Table 8. Colorectal cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Follow up duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Alkhenizan ¹⁹ 2007	Vitamin E alone Vitamin E as part of other supplements	Quant	≥18 y; range of pre-existing health states, but not high risk for colorectal cancer.	RCTs; Supplementation in capsule or tablet form; control = placebo or no intervention; reported total mortality, cancer mortality, cancer-specific mortality	2-4 depending on outcome	≥510 days - ≤10 y (not reported separately for individual cancers)	24,114 - 91,099 (across all trials, depending on analysis)	NR	1. CRC incidence (Vit E any combination) RR=0.95 (0.81-1.12) 2. CRC incidence (Vit E alone) RR=1.05 (0.79-1.39)	No evidence of protective effect of Vitamin E against CRC
Dubé ²³ 2007	ASA	Quant and Qual	"Average" risk	RCTs, controlled clinical trials	2 PHS 325mg every other day WHS 100mg/day	5-10	22,071-39,876	NR	1. CRC mortality (WHS) "No statistically significant benefit of ASA on CRC mortality" 2. CRC incidence RR=1.02 (0.84-1.25) 3. Adenoma incidence (PHS only) RR=0.86 (0.68-1.10)	Observational data appear to indicate that ASA use reduces the risk of colorectal neoplasia, but this effect is not seen in large trials of low dose ASA use

Table 8. Colorectal cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Follow up duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Browning ²⁰ 2006	Statins	Quant	All populations except highly specific statin-using patients (e.g. familial hypercholesterolemia, renal transplant)	RCTs; Control = placebo; Reported all cancer, site-specific cancer incidence or mortality	1-9 (depending on analysis)	Median followup: Trials: 3.6 y	RCTs: n = 103,573	RCTs: 18-82 y	CRC incidence from use of statins: 1. All studies RR=1.02 (0.89-1.16) 2. Mortality (1 trial) RR=0.33 (0.07-1.63) 3. LI (4 trials) RR=1.0 (0.85-1.18) 4. LO (5 trials) RR=1.04 (0.85-1.30) 5. LP (2 trials) RR=1.07 (0.61-1.85) 6. MP (5 trials) RR=1.04 (0.84-1.30) 7. HP (2 trials) RR=0.99 (0.83-1.18)	No evidence of protective effect

Table 8. Colorectal cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Follow up duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Type of intervention: Population-based screening										
Hewitson ²⁴ 2006	FOBT (Hemoccult) investigation following positive screen result – colonoscopy or sigmoidoscopy and double contrast barium enema, with removal of colorectal cancers or adenomas found at diagnostic investigation	Quant, Qual	Adults; volunteers or individuals/households identified from primary care records or population registries	RCTs (individual or groups); control = no screening; report results based on participation in >1 screening round; report colorectal cancer mortality	4	10-17	46,551-150,251 Total 329,642	45-80 y	1. CRC mortality (all groups) RR=0.84 (0.78-0.90) 2. CRC mortality (biennial screening groups) RR=0.85 (0.78-0.92) 3. All cause mortality (all groups) RR=1.00 (0.99-1.01) 4. All cause mortality without CRC mortality (all groups) RR=1.01 (1.00-1.03). 5. CRC mortality (attended ≥1 screening) RR=0.75 (0.66-0.84)	15-16% reduction in relative risk of CRC mortality for individuals allocated to receive screening, rising to 25% risk reduction for those who actually participated at least once. No evidence of reduction in overall mortality, and borderline evidence of increased non-CRC mortality

Table 8. Colorectal cancer preventive interventions (continued)

Study	Specific intervention(s) evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Follow up duration (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Kerr ²⁵ 2007	Once-only flexible sigmoidoscopy in addition to FOBT test, followed by colonoscopy for investigation of positive screen result	Quant	Not specified, but population-based implied	RCTs; control = no screening control for this study was FOBT alone	1	2-5	10,978	50-75	1. CRC mortality RR=0.78 (0.36-1.73) 2. CRC incidence RR=1.37 (0.88-2.15)	The trial was limited by short followup period and no repeat screening. Results do not support benefit of combined screening strategy of FS with FOBT over FOBT alone in asymptomatic populations Poor compliance with combined screening group

Table 9. Prostate cancer preventive interventions

Study	Specific interventions evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type trials	Followup durations (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Type of intervention: Chemoprevention										
Bardia ¹⁸ 2008	Antioxidant supplementation: β-carotene Selenium Zinc Vitamin C Vitamin E or any others	Quant	People at average risk of cancer	RCTs; Supplements with fully disclosed components and not dietary increases in nutrients; placebo-controlled; ≥1 y of followup; reported overall cancer incidence	≤12	NR	55,709 (total over all trials)	NR	Prostate cancer incidence: Any antioxidant RR=0.87 (0.74-1.02) Selenium alone (200µg daily): "decreased incidence". [Estimated RR ²⁶ =0.37 (0.20-0.70)]	No evidence of protective effect of antioxidants on prostate cancer risk

Abbreviations: NR=not reported; Quant=Quantitative

*This review also reported data relating to antioxidants; not included under this review's data as included in more recent included review¹⁸

Table 9. Prostate cancer preventive interventions (continued)

Study	Specific interventions evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type trials	Followup durations (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Alkhenizan ¹⁹ 2007	Vitamin E alone Vitamin E as part of other supplements	Quant	≥18 y; range of pre-existing health states, but not high risk for prostate cancer.	RCTs; Supplementation in capsule or tablet form; control = placebo or no intervention; reported total mortality, cancer mortality, cancer-specific mortality	2-4 (depending on outcome reported)	≥510 days - ≤10 y (not reported separately for individual cancers)	24,114-71,759 (total over all trials analyzed, depending on outcome reported)	NR	Prostate cancer incidence: 1. Any dose/combination RR=0.85 (0.74-0.96) 2. Vit E alone RR=0.86 (0.70-1.06) 3. Vit E plus other supplements RR=0.79 (0.67-0.93) 4. Vit E ≥300mg/day RR=0.94 (0.79-1.11) 5. Vit E <300mg/day RR=0.69 (0.55-0.87)	Vitamin E may be protective against prostate cancer
Bristol SLR Team ²⁶ 2006	Calcium supplements	Quant	NR; presumed cancer free	All	1 RCT	11 (intervention duration plus followup)	672	61.8 (mean)	RR=0.83 (0.52-1.32)	No evidence of protective effect of calcium supplementation

Table 9. Prostate cancer preventive interventions (continued)

Study	Specific interventions evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type trials	Followup durations (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
Browning ²⁰ 2006	Statins	Quant	All populations except highly specific statin-using patients (e.g. familial hypercholesterolemia, renal transplant)	RCTs; Control = placebo; Reported all cancer, site-specific cancer incidence or mortality	1 or 4 (depending on analysis)	Median followup: Trials: 3.6 y Observational studies: 6.2 yrs	RCTs: n =103,573 Observational studies: n=826,854	RCTs: 18-82 yrs Observational studies: 30-89 yrs	1. Prostate cancer incidence RR=1.00 (0.85-1.17) 2. Prostate cancer mortality (1 trial) RR=0.99 (0.14-7.01)	No evidence of protective effect
Type of intervention: Screening										
Ilic ²⁷ 2007	Any of PSA DRE TRUS biopsy	Quant	All men	RCTs, quasi-randomized, controlled trials; screening versus no screening	2 RCTs Quebec Annual screening Round 1 = PSA + DRE + TRUS where PSA >3.0ng/ml and/or abnormal DRE Later rounds = PSA with TRUS biopsy of PSA >3ng/ml or increased	11-15	9,026-46,486 Total 55,512	45-80	Prostate cancer mortality RR=1.01 (0.80-1.29)	Insufficient evidence to either support or refute the routine use of mass, selective, opportunistic, or no screening to reduce prostate cancer mortality

Table 9. Prostate cancer preventive interventions (continued)

Study	Specific interventions evaluated	Type of SR	Eligible populations	Eligible study designs	Number and type of trials	Followup durations (years)	Sample sizes	Ages	Summary effect sizes	Main conclusion
					by >20% 3-ylly screening Rounds 1&2=DRE Rounds 3&4=DRE + PSA. TRUS biopsy if DRE abnormal or PSA >4.0ng/ml					

*This review also reported data relating to antioxidants; please refer to more recent review included above¹⁸

Table 10. Details of family history and personalized risk interventions

Study and study design	Target population	Target behavior	Family history collection component of intervention	Risk personalization component of intervention	Other components	How individualized risk reduction advice communicated
Curry ⁴⁹ 1993 RCT	Women eligible for SM	Having SM	Mailed self-completion questionnaire: 1. Information on 1DR and 2DR with BC 2. Other risk factors: age, age at menarche, age at first birth, menopause status, age at menopause, previous mammography, history of biopsy	Insertion of following text into a generic mammography invitation letter: "BC affects 1 in 10 women over their lifetime, but is more common with a personal history of particular risk factors. The recommendation that you schedule a comprehensive visit now is based on the answers you provided on the BC Screening Survey. From your responses, we were able to determine that your personal screening schedule is affected by your age [plus other risk factors if present]..."	None	Letter
Giles ⁴⁸ 2001 BA	General female population	Having SM BSE CBE	Interviewer-administered survey: 1. Number of 1DRs with BC 2. Other risk factors: age at menarche, age at first live birth, number of breast biopsies 3. Other: history of practicing BSE, formal instruction in BSE, confidence in performing BSE, history of mammography	1. RR for developing BC in next 5y 2. RR for developing cancer in her lifetime	Encouragement to follow ACS guidelines for mammography, BSE, CBE ACS instruction card on BSE NCI brochure on BC risk factors	Individual consultation with a pharmacist

Abbreviations: 1DR=first degree relative; 2DR=second degree relative; ACS=American Cancer Society; BA=before-after; BC=breast cancer; BSE=breast self-examination; CBE=clinical breast examination; FH=family history; NCI=National Cancer Institute; RCT=randomized controlled trial; RR=relative risk; SM=screening mammogram;

Table 10. Details of family history and personalized risk interventions (continued)

Study and study design	Target population	Target behavior	Family history collection component of intervention	Risk personalization component of intervention	Other components	How individualized risk reduction advice communicated
Bastani ⁵⁰ 1999 RCT	Female relatives of breast cancer patients	Having SM	Current age age at menarche, age at first live birth, number of breast biopsies, and number of first-degree relatives with breast cancer age at first biopsy, age of the index case (first degree relative listed in cancer registry) with cancer, age at menopause	List of personal risk factors for breast cancer and classification of risk in comparison with other women of the same age (“slightly”, “moderately”, or “substantially” higher risk)	Other materials tailored for high-risk women” plus message regarding the importance of regular screening mammography	Letter

Table 11. Evaluations of family history and personalized risk

Study and study design	Participants	Control intervention/group	Outcome measure(s)	Effect of FH based intervention on target behavior(s)	Modified Jadad quality score (max=8)	Conclusions
Curry ⁴⁹ 1993 RCT	Women ≥50 y registered with a single HMO, eligible for SM n=2,076	1. No risk data captured, generic invitation to schedule a mammogram (C1) 2. No risk data captured, general risk information included in invitation to schedule a mammogram (C2) 3. Risk data captured, general risk information included in invitation to schedule a mammogram (C3)	Having a mammogram within 12 months of invitation	% Received a mammogram by 12 months: I: 44.6% C1: 49.2% C2: 41.1% C3: 41.8% P=0.23 (χ^2) Comparison restricted to I&C3 only (risk factor questionnaire plus general risk or personalized risk invitation), stratified by family history: No family history – I: 39.7% C3: 41.4% Positive family history: I: 66.7% C3: 42.9% P=0.005. No significant interactions of personalized feedback with other risk factors	4 Allocation concealment NR	Overall, capturing risk information and/or addition of general or personalized risk information to screening mammography invitations did not increase uptake. Findings suggest that capturing risk information and personalizing risk messages may be more effective in promoting screening behavior

Abbreviations: 1DR=first degree relative; BA=before-after; BC=breast cancer; BSE=breast self-examination; CBE=clinical breast examination; FH=family history; NA=not applicable; NR=not reported; RCT=randomized controlled trial; SM=screening mammogram;

* Confidence intervals not provided in original article, calculated on basis of data presented

Table 11. Evaluations of family history and personalized risk (continued)

Study and study design	Participants	Control intervention/group	Outcome measure(s)	Effect of FH based intervention on target behavior(s)	Modified Jadad quality score (max=8)	Conclusions
Bastani ⁵⁰ 1999 RCT	Women with a 1DR with BC n=901	1. Note thanking for participation in telephone survey 2. General information booklet on BC	SM measured by self-report at 1 y followup	% Had SM All ages: <u>Baseline</u> I: 55.0% C:54.9% <u>Followup</u> I: 65.2% C: 57.7% P=0.05 30-40 <u>Baseline</u> I: 41.4% C:31.4% <u>Followup</u> I: 49.4% C:35.7% P=0.66 40-50 <u>Baseline</u> I: 61.4% C: 57.4% <u>Followup</u> I: 62.3% C:67.0% P=0.26 50-64 <u>Baseline</u> I: 58.9% C:68.8% <u>Followup</u> I: 76.8% C: 68.8% P=0.02	4 Allocation concealment NR	In a somewhat selected group of participants, and compared with the control intervention of FH taking and general information on BC, the active intervention of FH taking accompanied by individualized risk assessment and reinforcement of importance of target behavior appeared to improve adherence with screening recommendations to a modest level, equivalent to difference in increased uptake by 7% in absolute terms No comparison group which did not have FH information collected

Table 11. Evaluations of family history and personalized risk (continued)

Study and study design	Participants	Control intervention/group	Outcome measure(s)	Effect of FH based intervention on target behavior(s)	Modified Jadad quality score (max=8)	Conclusions
Giles ⁴⁸ 2001 BA	Women ≥18y visiting a community pharmacy or attending a health screening event n=188	None	Adherence with ACS guidelines for BSE, CBE, and mammography, assessed at 6 months	Proportions following ACS guidelines (self- report) (% (95% CI*)) BSE All: Pre: 42/137 (31 (23-38)) Post: 77/137 (56 (48-64)) P<0.001 5 y risk≥1.7%: Pre: 4/20 (20 (2-37)) Post: 12/20 (60 (38-81)) P<0.005 CBE All: Pre:121/140 (86 (81-92)) Post:128/140 (91 (87-96)) P<0.09 5 y risk≥1.7%: Pre: 17/21 (81 (61-98)) Post: 17/21 (81 (64-98)) P=1.00 Mammography All: ≥50y	NA	Findings suggest that personalized risk assessment which included family history may improve adherence with recommended screening practices The size and direction of changes were different across the three target behaviors and no uniform effect was observed in high risk participants The lack of a control intervention, the reliance on self-report data, and the small sample size for sub- group analyses severely limit the conclusions which can be drawn

Table 11. Evaluations of family history and personalized risk (continued)

Study and study design	Participants	Control intervention/group	Outcome measure(s)	Effect of FH based intervention on target behavior(s)	Modified Jadad quality score (max=8)	Conclusions
				Pre: 33/44 (75 (62-88)) Post: 31/44 (70 (57-84)) P<0.48 40-49 Pre: 18/32 (56 (39-73)) Post: 21/32 (66 (49-82)) P<0.257 5 y risk≥1.7%: Pre: 17/21 (81 (64-98)) Post: 15/21 (71 (52-91)) P<0.317		

Table 12. Harm/risk of family history collection

Author Year Setting	Type of cancer	Study design	Characteristic of population	1. No.recruited 2. No.completed	Time points for analysis (months)	Duration of intervention followup	Who delivered intervention?	Method of family history collection	Other intervention(s)
Leggatt ⁵¹ 2000	Colorectal/ colon/rectal Breast	Before - After uncontrol led study	Unselected patients aged 35 to 65 years	1. 666 (29% response) 2. 604	Baseline 1-1.5	Postal survey followed by single session	Lower risk group: letter from family doctor Potential increased risk groups: family doctor and/or oncologist/ geneticist	Postal cancer family history questionnaire	Participants provided with risk information

Chapter 4. Discussion

The purpose of this review was to establish the evidence base to answer the question, “In relation to the cancers of interest, would routinely taking and using family history for risk assessment in primary care settings be likely to lead to net health benefits?” Acknowledging the scope of this question, the evidence was assembled across a number of subsidiary questions, addressed individually below.

Throughout the review, the focus was the primary care context. This led to two decisions which underpinned the review’s methodology, specifically the eligibility criteria. Firstly, across all questions, the populations studied had to reflect primary care populations. In practice, this meant that populations who already had cancer, a pre-cancerous condition, or who were suspected of carrying a genetic risk, were excluded. Secondly, studies of family history taking as a primary care intervention, i.e., *as an intervention in and of itself*, were included, but those where family history taking was approached as a specialist activity, and/or embedded within a larger set of clinical activities such as assessment for genetic testing, were excluded.

We also drew a distinction between “taking family history” *as a distinct activity* practiced by health care providers (of central interest in this review) and “being aware of a positive family history” *as an attribute* of study participants. A patient’s ability to accurately report family history information is a prerequisite for valid family history collection. However, some people may also have a pre-existing perception of an unusually high family prevalence of cancer, leading to this being itself a cause of anxiety, quite separate from any effect of the clinical activity of taking a family history. Thus, evaluations of family history taking as an intervention need to be carefully designed to take account of this complicating factor.

Risk Stratification Algorithms

Many cancer risk stratification algorithms, models and systems exist, and the goal of this review was to identify which of those, based on family history information, performed well in primary care type populations. In approaching this question, we sought to identify evaluations of frameworks devised specifically for primary care, or which might be transferable to primary care even if originally designed for other purposes.

Further, we were interested in evaluations which assessed the ability of a system to correctly predict risk in *individuals*, not simply on studies of overall associations between family history and disease incidence at a population level. As explained in Chapter 3, to be suitable for implementation in routine clinical settings, a risk prediction system needs to differentiate between the disease risk of individuals, such that it consistently predicts higher risk of cancer in those who are truly destined to go on to develop the disease than in those who will not.

Review question (Q) 1 was therefore tightly focused on evaluations of models predicting individual risk, and this led to the exclusion of a large number of analytical epidemiological reports, descriptive clinical studies, and validation studies of models which did not present data on individual discriminatory accuracy (e.g., Constatino et al., 1999⁸⁴). We were able to identify evaluations of only two distinct approaches, one a family of models based on the Gail model¹⁵ (developed for breast cancer risk prediction), and the Harvard Cancer Risk Index¹⁶ (designed to predict the risk of a range of cancers, although validation data were available only for CRC). Both included a range of variables in addition to family history.

The Gail model is publicly available on the National Cancer Institute's web site (www.cancer.gov/bcrisktool/). It should be noted that its original purpose was epidemiological – to facilitate the design of clinical trials by permitting sample size calculations to be based on improved assumptions about expected disease outcome rates – rather than for clinical decisionmaking.¹⁵ Evaluations of this model indicated excellent performance at the population level, i.e., calibration, for predominantly white U.S. and Italian populations, judged by the ratio of expected to observed cases in the population studied. The model performed less well in more diverse U.S.¹³ or African American¹⁰ populations. The CARE model also showed good calibration.⁷

However, for all of these models, evaluations indicated generally modest discriminatory ability, with the c-statistic ranging from 0.55-0.59. Many women who would be judged to be high risk by one of these models would not go on to develop breast cancer, and vice versa.

As a contrast, family history-based risk stratification has been found to perform much better as a predictor of coronary artery disease, with a c-statistic of 0.87.¹⁷³ While family history can provide some useful predictive information on some common health conditions, the situation for breast cancer is less clear-cut. Although there are breast cancer family syndromes, these are associated with only about 5 percent of breast cancer cases. Over ninety percent of the incidence of breast cancer at a population level is not associated with a distinct familial pattern, and many women appear to develop breast cancer 'out of the blue'. The known general risk factors – e.g., younger age at menarche, and later age at birth of first child – each contribute only a little to overall incidence of the disease (individual relative risks are modest), and they are reasonably prevalent in most populations

Had the review found greater evidence of adequate discriminatory accuracy for some of these tools, this would not guarantee that their use would lead to better health outcomes in practice. A number of other conditions would need to be satisfied, for example evidence that different risk categories are matched with evidence on appropriate risk-specific preventive interventions. We note, for example, that the Gail and related models have been used primarily for assessing eligibility for cancer chemoprevention trials, although their use as more general clinical predictive tools is implied by their wider availability to the professional community and the general population. Stronger evidence is needed on the application of the tools in settings closer to routine clinical practice, and trials are required which directly assess the outcomes from risk assessment combined with risk-appropriate preventive interventions, not just assessments of the technical accuracy of risk prediction. Also, the use of tools needs to take into account standard of practice for the particular clinical context. As a hypothetical example, if guidelines were to recommend colonoscopy and polypectomy for all individuals with a family history of colorectal cancer, and this was widely implemented, and it led to a reduction in absolute colorectal cancer rates in the general population, then evaluations of risk prediction algorithms would need to consider the power implications of using cancer incidence as a primary outcome.

Since the overall purpose of this review was to assess elements of the clinical utility of family history taking, we would ideally have liked to evaluate cancer risk stratification systems based solely on family history. At the time of writing, perhaps the prototypical system of interest is Family HealthwareTM,¹⁷⁴ a Web-based tool designed to assess a person's familial risk for coronary heart disease, stroke, diabetes, and colorectal, breast, and ovarian cancer. It also provides users with personalized recommendations for lifestyle changes and screening. At the time of writing, evaluation data for this tool were not available.

In the absence of validation studies of family history-based systems, we extended the review to include tools with a family history component. Despite this, a large number of predictive tools were excluded, either because they did not include any history items, some items would not be available for all patients, or would not routinely be available to a primary care practitioner. Further details of the wider range of risk prediction systems can be found at http://riskfactor.cancer.gov/cancer_risk_prediction/.

Cancer Prevention Interventions

Review (Q2) was an assessment of the overall benefits and harms of available preventive interventions for breast, ovarian, colorectal, and prostate cancers. As noted in Chapter 1, answering this question was an essential step in addressing the overall question of clinical utility of cancer family history taking, but cancer prevention in general was not the primary focus of this report. With a focus on published reviews of evidence, we again applied the criterion of primary care applicability in terms of unselected populations, which would be expected to contain individuals at high, medium, and low risk. Reviews were excluded only where they specifically focused on studies of high risk populations such as those affected by cancer or known pre-cancerous conditions, or people at known or suspected high risk of an inherited genetic disorder. Thus, while all reviews focused on “general” populations, *none* specified having relatives with cancer (but not suspicion of inherited genetic disorder) as an exclusion criterion. Most did not in fact specify this one way or the other, except one²³ which explicitly stated that studies with participants with a positive family history of cancer were eligible. In the end, none of the reviews actually reported results separately for studies of participants with affected relatives, likely reflecting a lack of such primary studies.

We also decided to focus on reviews of intervention studies, noting (for example) how apparently clear-cut evidence from observational epidemiological studies in the areas of beta-carotene and lung cancer⁷¹⁻⁷³ and hormone replacement therapy and breast cancer¹⁷⁵ has been contradicted by subsequent randomized controlled trials.^{74,176} Where more than one eligible review was identified, we included the data from the most recent and highest quality review. We found no reviews relating to primary or secondary prevention of ovarian cancer.

With respect to primary prevention of the cancers of interest, we found a striking lack of experimentally-derived evidence. We do not suggest, however, that this lack of evidence of effectiveness means that the interventions examined are ineffective. A number of issues and limitations must be considered.

Firstly, there is the difficulty of translating the exposures examined in many observational studies into implementable interventions in trial settings. Observations on the potential protective effect of specific antioxidants, micronutrients, and vitamins have generally been derived from analyses of dietary habits or supplements containing multiple vitamins and minerals, whereas intervention studies generally investigated the effects of one or two supplemental agents in factorial trials. Moreover, in some instances, notably the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, the doses of these agents were substantially higher than the exposures obtained through dietary and multivitamin supplements. Hence, few intervention trials have investigated ‘whole diet interventions’. To take calcium as an example, pooled analyses of cohort studies indicate an approximately 15 percent reduction in risk of colorectal neoplasia associated with higher dietary calcium intake,⁴⁵ but no reviews were available of dietary calcium as an intervention in cancer prevention. Also, chemoprevention interventions may act early in

cancer development, meaning that preventive effects may only be observable in long-term studies, not reflected in the followup timing reported in many of the primary trials contained in the reviews.

A second issue is the baseline population risk, and the power of meta-analyses to detect an intervention effect. Taking calcium as an example again, we note that reviews which have conducted pooled analyses of studies conducted in higher risk populations (e.g., patients with adenomatous polyps, therefore excluded from the present review) have demonstrated an apparent 20 percent lower recurrence rate amongst those randomized to calcium supplementation than those on placebo.¹⁷⁷ It is perhaps worth noting that evidence of possible preventive effects of vitamin E¹⁹ and of calcium²⁶ was noted in relation to prostate cancer; although the latter review met our (Q2) eligibility criteria in that the primary studies had recruited participants not at high risk for prostate cancer, the data came from a secondary analysis of a study with participants at elevated risk of colorectal cancer (the prostate outcomes being a secondary analysis).⁴⁷ There is a current stream of thinking suggesting that there may be some common etiological pathways for prostate and colorectal cancer.^{178,179} This might mean that these apparently unselected participants were *de facto* at elevated risk of prostate cancer because they were at elevated risk of colorectal cancer.

The focus on reviews also meant that we did not include large primary studies of interventions which have not yet been the subject of reviews. The report finds itself in the anomalous situation where some included reviews were based on analyses of single trials (and therefore, effectively present single trial data), but where interventions evaluated in large single trials were excluded on the basis of ineligible design (i.e., not a review). It was not possible, at the outset, to predict the results of the literature search for review (Q2) and to anticipate this situation. Extending (Q2) to include primary studies would have been a significant undertaking and was beyond the resources available for this review. We acknowledge that this has probably resulted in the exclusion of data on cancer prevention interventions which suggest protective effects. For example, one study¹⁸⁰ was legitimately excluded, which reported a large combined analysis of two selected RCTs along with a systematic review restricted to observational studies. This study was not eligible because the systematic review element excluded intervention studies, and the two RCTs reported represented selective reporting of all relevant trial evidence. The two RCTs were designed primarily to assess the effects of acetylsalicylic acid (ASA) on non-cancer outcomes^{181,182} but had extended followup to examine the effects on cancer.¹⁸⁰ The pooled analysis of the two trials (ASA assigned at doses of 300mg, 500mg or 1200mg per day) suggested a protective effect on colorectal cancer incidence at ten years (pooled relative risk 0.74 (95 percent CI 0.56-0.97)). The magnitude of effect was consistent with observational studies, and no effect on the incidence of other types of cancer was observed.

Despite extensive investment in cancer research over the last four decades, underlying mechanistic pathways for individual cancers still remain to be fully elaborated. Thus, the 'risk factor' approach of many analytical observational studies is an insufficient basis for drawing definitive conclusions on biological mechanisms of cancer causation and prevention. Emphasis is now being placed on large-scale prospective cohort studies with associated biobanks that hold promise of improved exposure assessment, and that will enable joint effects of genes and exposures to be investigated with adequate statistical power.¹⁸³

The evidence regarding screening for the cancers of interest provided greater clarity than that for primary prevention. As for secondary prevention, we found no reviews of screening or surveillance interventions relating to ovarian cancer. Regarding breast cancer, there appears to be

clear evidence, on the basis of a pooled analysis of three large population-based trials, that teaching women breast self-examination and encouraging them to carry it out regularly has no measurable effect on breast cancer mortality. In some countries, the emphasis has shifted from exhorting women to examine their breasts monthly to becoming ‘breast aware’ – being familiar with what is ‘usual’ over a monthly cycle and therefore being able to identify and act on what is not ‘normal’.¹⁸⁴

A large number of reviews of population-based mammography screening have been conducted, and the evidence seems to suggest that it reduces breast cancer mortality by about 15 percent. The evidence is most clear cut for women aged 50 and over, the impact being limited in younger women by greater breast density and lower baseline risk. There is debate about the validity of using cancer-specific mortality as the primary outcome for evaluations of mammography screening; arguments revolve around the possibility of bias in the coding of death between screened and control populations, and the notable lack of impact of screening on all cause mortality. Where trials have demonstrated a reduction in mortality, there is no suggestion that annual screening offers benefits over biennial screening in women aged 50 or older. This also holds for younger age groups, although the lower sensitivity of the test and evidence of the more rapid growth of tumors in younger women have led some experts to suggest more frequent screening to maximize sensitivity.^{185,186}

Regarding colorectal cancer, the evidence appears to indicate that fecal occult blood testing (FOBT) and followup with colonoscopy reduces colorectal cancer mortality. The very limited evidence (one trial) suggests that flexible sigmoidoscopy does not improve this outcome, and there is no consensus on the optimum screening interval. Observers have also noted the lack of impact of screening on overall mortality, and some analyses have indicated an increase in non-colorectal cancer mortality. Although a 2008 U.S. Preventive Services Task Force (USPSTF) report¹⁸⁷ contains a Grade A recommendation which includes colonoscopy as a screening intervention for colorectal cancer in individuals aged 50-75 years, the background evidence report¹⁸⁸ indicates that no trials of colonoscopy as a stand-alone screening intervention were identified.

We found no evidence of an effect of prostate specific antigen (PSA)-based screening strategies on prostate cancer mortality. In a recent USPSTF review, two RCTs were identified that did not show a mortality benefit from PSA screening independently or in a meta-analysis; important flaws in design and analysis were noted.¹⁸⁹ The USPSTF review also identified one cross-sectional and two prospective cohort studies of possible psychological effects of PSA screening results. These suggested that false-positive PSA screening results cause psychological adverse effects for up to 1 year after the test.

Although we sought reviews of ultrasound screening for ovarian cancer as an intervention, we did not consider reviews of other interventions such as CA-125 screening. In retrospect, it would have been legitimate to include this since the report also reviewed PSA-based screening for prostate cancer, which is an analogous serum-based cancer screening test. We note that the USPSTF positively recommended against screening general using CA-125 in a 2004 report,¹⁹⁰ suggesting that the possibility of earlier detection would lead to small effects, at best, on mortality (because of the low prevalence of ovarian cancer therefore low positive predictive value), and fair evidence of important harms because of the invasive nature of diagnostic investigations.

We also did not review genetic testing as an intervention, considering this not to be in itself a preventive intervention, but we did include the broader interventions of referral for genetic

counseling and/or testing as interventions of interest applied to populations not considered high genetic risk. However, no reviews on these interventions were identified.

Family History-Based Risk Assessment and Individual Preventive Behaviors

It is postulated that knowing one's genetic risk of disease, whether through a genetic test or family history, can provide a motivation to comply with advice on preventive interventions¹⁹¹ and some descriptive studies suggest that people who have a family history are overrepresented in studies of screening adherence.¹⁹²⁻¹⁹⁸ Noting concerns discussed in Chapter 1 about distinguishing between the behavior of people motivated by pre-existing perceptions of elevated disease risk because of living with a "family disease" from the effects of family history-based clinical strategy, we focused on intervention studies where the effects of confounding would be less evident. We found only three relevant primary studies, all of them relating to breast cancer prevention. One of them sampled women known to have a first degree relative with breast cancer⁵⁰ (although not, by definition, formally identified as being at elevated genetic risk themselves), one was health organization-based,⁴⁹ and the third likely comprised participants who were more than typically interested and generally compliant with some screening recommendations.⁴⁸ The only study which in any way replicated a primary care consultation involving personal interaction between a health care professional and an individual patient was the third of these studies, which was in the setting of a community pharmacy,⁴⁸ but was limited by its uncontrolled design. The participants appeared to have had an atypically high average adherence rate with screening mammography recommendations at baseline, which could have resulted in apparent lack of effect because there was little room for improvement (a possible "ceiling effect"). The overall evidence was therefore equivocal, neither confirming nor undermining the hypothesis that systematic feedback of risk motivates compliance.

Direct Harms or Risks From Family History-Based Risk Assessment

All health care interventions should be assessed for evidence of harm as well as benefit. We identified only one study relevant to family history taking that was conducted in an unselected primary care population. The respondents who were not found to be at elevated cancer risk had no evidence of adverse psychological outcomes, and in fact there was some indication that the assessment was beneficial in that it promoted more realistic personal risk perceptions. In contrast, participants whose initial assessments indicated potential elevated risk had higher baseline anxiety levels than those whose initial assessments indicated population risk, irrespective of their final risk assessment. In other words, both "true positives" and "false positives" had higher average pre-test anxiety levels which might suggest that perception of family history-associated cancer risk (whether confirmed or not) rather than collection of family history information might be associated with higher levels of anxiety.

This single study is insufficient to conclude that family history taking as a deliberate clinical strategy is, in itself, likely to be harmful in terms of emotional impact, but it is consistent with findings from studies of genetic testing. It suggests that assessments of psychological status might be appropriate before embarking on family history-based risk assessments in order to identify those individuals who might be most at risk of ongoing anxiety or cancer-related worry,

and who might therefore warrant extra support or counseling, irrespective of their actual assessed disease risk.

Limitations

The eligible studies within this systematic review were limited to primary studies and systematic reviews in the English language. We restricted the search of systematic reviews to 2003 forward, to ensure that only relatively recent reviews were selected. The review was also limited to studies in adults; therefore no conclusions can be drawn with respect to children or young people specifically.

The effectiveness of family history-based tools and interventions are dependent on the accuracy of reporting of family history, and it is impossible to comment on this aspect of the topic. We did not restrict studies according to the manner in which cancer family history was collected and considerable variation in the methods used was observed. Almost universally, studies depended on self-report methods and are therefore dependent on the individual respondents' knowledge of their history. This represents a limitation on family history taking in practice rather than a limitation specifically of the review, and was explored in a previously published review.⁵

In examining the effects of family history taking on behavior (Q3), the eligibility criteria specified the intervention as feeding back family history-based risk alone, or with risk advice. We did not examine taking family history itself as an intervention without some element of feedback to a patient. The studies identified also evaluated interventions which were not terribly reflective of day-to-day primary care practice. It is therefore impossible to comment on whether the capture of family history information might lead a practitioner to consider different preventive strategies, or the incorporation of family history information into the broader knowledge of a patient might lead to changes in the nature or emphasis of preventive advice which is offered. The emphasis on very specific clinical behavioral outcomes also does not allow for exploration of other effects on the part of patients, e.g., seeking out more extensive information from family members as a result of having been asked "the first" set of questions on family history.

In regard to cancer prevention interventions, we were able to provide only an overview of classes of interventions and could not examine differences in their individual implementation (e.g., different doses). For reviews that assessed the same intervention, we selected the single best review based on several factors including number of studies and year of publications and methodological quality of the review.¹⁷ We did not contact authors for additional clarification for QUOROM requirements. Neither did we re-abstract or re-analyze original randomized trials eligible within the systematic reviews. In addition, as discussed above, the emphasis on reviews inevitably resulted in the exclusion of RCTs which had not been incorporated into reviews, including large studies such as the Women's Health Initiative trial of a dietary modification program on the incidence of colorectal cancer in post-menopausal women.¹⁹⁹ We believe that, where interventions have been evaluated in primary trials which have then been included in published reviews, we have captured and reported the effectiveness evidence objectively; however, we believe that relevant effectiveness evidence for some interventions, based on well-designed trials, has been missed wholesale because primary intervention studies were not eligible for (Q2).

Conclusions

1. The evidence for the predictive accuracy of algorithms in primary care populations was very limited. Although many tools were identified that incorporated some family history information, no evaluations of solely family history-based tools were identified. The tools on which it was possible to comment related mainly to breast cancer.

Recommendations for future research:

- The actual performance of tools based only on family history should be formally examined in primary prospective studies, and/or in secondary analysis of large cohort studies.
- The performance of individual family history components of different risk stratification models which use a wider range of factors (including those examined in this report) should be examined separately from the non-family history components, in order to determine whether they provide sufficient predictive power in the absence of the non-family history factors.
- For clinical relevance, the focus of validation should be discriminatory accuracy at the individual patient level.
- More definitive evaluation should examine the effect on health outcomes when risk stratification systems are used in combination with preventive interventions, in actual practice settings. This cannot be done with secondary analyses of observational data and requires well-designed intervention studies.

2. The evidence establishing the efficacy of interventions for primary and secondary prevention based on systematic reviews of randomized or controlled clinical studies in unselected populations is very limited. Interventions for which there were reviews include chemoprevention (antioxidants, calcium, NSAIDs, and statins) and screening interventions (BSE, mammography, FBOT, flexible sigmoidoscopy, and PSA) for breast, colorectal and prostate cancers. No reviews were found for ovarian cancer. It is likely that this review excluded effectiveness data available from RCTs of interventions which have not yet been the subject of systematic reviews.

Recommendations for future research:

- The large amount of evidence on potential primary cancer preventive interventions obtained from observational studies of cancer risk factors should continue to be further evaluated in well-designed randomized controlled trials.
- Further systematic reviews should be conducted to examine the full range of potentially preventive interventions

3. Within primary care populations, there is very limited evidence to support or refute the effect on risk-reducing behavior changes (e.g., lifestyle changes or uptake of recommended clinical interventions) of taking a family history and using it to personalize risk of breast, ovarian, colorectal, or prostate cancer.

Recommendations for future research:

- Well-designed trials are required that compare family history-based, personalized risk advice with standard of care on risk reducing behaviors in populations at different risk levels (including population risk).

4. In primary care populations, there is very limited information to evaluate direct harm incurred from the routine practice of taking family history and using it to personalize risk information.

Recommendations for future research:

- Trials of family history taking as an intervention should include capture of data to examine the full range of potential impacts on individuals. Baseline data on psychological status should be captured so that this can formally be adjusted for in outcome analyses.

5. Research on the use of family history tools, risk stratification systems, and family history-based personalized prevention advice should take into account evidence on the factors likely to promote their effective use in practice, such as the educational needs of primary care practitioners and issues which act as barriers or constraints to their implementation in practice.

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Appendix A – Search Strategies Detailed

Question 1

Ovid-MEDLINE

1. claus.tw.
2. gail.tw.
3. BRCAPRO.tw.
4. BOADICEA.tw.
5. UK cancer family study group.tw.
6. UKCFSG.tw.
7. Myriad.ti,ab.
8. tyrer Cuzick.ti,ab.
9. ((Amsterdam or Bethesda or Manchester or Gilpin or Evans or Frank or Finnish or Yale or Spanish) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
10. FHAT.ti,ab.
11. (Australia adj5 breast cancer cent\$).tw.
12. couch.ti,ab.
13. ((mendel or LAMBDA) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
14. (Dutch guideline adj7 breast).ti,ab.
15. (nice guideline? and breast cancer).ti,ab.
16. or/1-15
17. models, statistical/
18. models, theoretical/ or models, genetic/
19. 17 or 18
20. genes, brca1/ or genes, brca2/
21. BRCA\$.tw.
22. 20 or 21
23. 19 and 22
24. 16 or 23
25. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
26. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
27. *Neoplasms/
28. or/25-27
29. validation.ti.
30. accuracy.ti.
31. validation studies/
32. evaluation studies/
33. exp "Sensitivity and Specificity"/
34. "reproducibility of results"/
35. odds ratio/
36. multivariate analysis/
37. exp Probability/

38. predictive value?.ti,ab.
39. or/29-38
40. 24 and 28 and 39
41. animals/ not (humans/ and animals/)
42. 40 not 41
43. limit 42 to english language
44. limit 43 to yr="1990 - 2008"
45. Breast Neoplasms/
46. exp Colorectal Neoplasms/
47. exp Prostatic Neoplasms/
48. exp Ovarian Neoplasms/
49. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
50. or/45-49
51. exp Mass Screening/
52. (surveillance or screening).ti.
53. Primary Prevention/
54. Preventive Medicine/
55. prophylactic.ti.
56. prevention.ti.
57. (genetic adj2 (counsel?ing or test\$)).ti.
58. Risk Assessment/
59. (risk adj (assessment? or stratification)).ti.
60. Preventive Health Services/
61. or/51-60
62. exp Pedigree/
63. limit 62 to humans
64. exp Medical History Taking/
65. ((family or familial) adj3 (histor\$ or history-taking or risk\$)).ti,ab.
66. anamnesis.ti.
67. (human adj2 pedigree).ti,ab.
68. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
69. genogram\$.ti,ab.
70. ((famil\$ or heredi\$ or inherit\$) adj3 (cancer\$ or carcinom\$ or neoplasm\$)).ti,ab.
71. (genetic adj2 (screening or test\$)).ti,ab.
72. Family Health/
73. or/63-72
74. exp Neoplasms/
75. (neoplasm? or carcinoma? or cancer?).ti.
76. 74 or 75
77. guideline.pt.
78. practice guideline.pt.
79. guideline?.ti.
80. or/77-79
81. 73 and 76 and 80
82. 50 and 61 and 80

83. 81 or 82
84. (note or comment or editorial).pt.
85. 83 not 84
86. limit 85 to english language
87. limit 86 to yr="2003 - 2008"
88. 44 or 87

Ovid-EMBASE

1. claus.tw.
2. gail.tw.
3. BRCAPRO.tw.
4. BOADICEA.tw.
5. UK cancer family study group.tw.
6. UKCFSG.tw.
7. Myriad.ti,ab.
8. tyrer Cuzick.ti,ab.
9. ((Amsterdam or Bethesda or Manchester or Gilpin or Evans or Frank or Finnish or Yale or Spanish) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
10. FHAT.ti,ab.
11. (Australia adj5 breast cancer cent\$).tw.
12. couch.ti,ab.
13. ((mendel or LAMBDA) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
14. (Dutch guideline adj7 breast).ti,ab.
15. (nice guideline? and breast cancer).ti,ab.
16. or/1-15
17. MATHEMATICAL MODEL/ or STATISTICAL MODEL/ or CANCER MODEL/ or GENETIC MODEL/
18. GENETIC ALGORITHM/ or ALGORITHM/
19. or/17-18
20. Brca1 Protein/ or Brca2 Protein/
21. oncogene/
22. brca2 gene/
23. BRCA\$.tw.
24. or/20-23
25. 19 and 24
26. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
27. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
28. *Neoplasms/
29. or/26-28
30. 16 or 25
31. 29 and 30
32. validation.ti.
33. accuracy.ti.

34. agreement.ti.
35. VALIDATION STUDY/ or INSTRUMENT VALIDATION/ or VALIDATION PROCESS/
36. diagnostic accuracy/
37. exp statistical parameters/
38. prediction/
39. "SENSITIVITY AND SPECIFICITY"/
40. predictive value?.ti,ab.
41. or/32-40
42. 31 and 41
43. limit 42 to human
44. limit 43 to english language
45. limit 44 to yr="1990 - 2008"
46. exp Neoplasms/
47. (neoplasm? or carcinoma? or cancer?).ti.
48. 46 or 47
49. exp Breast Cancer/
50. exp Colon Cancer/
51. exp Ovary Cancer/
52. exp Prostate Cancer/
53. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
54. or/49-53
55. exp anamnesis/
56. ((family or familial) adj3 (histor\$ or history-taking or risk\$)).ti,ab.
57. anamnesis.ti.
58. (human adj2 pedigree).ti,ab.
59. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
60. ((famil\$ or heredi\$ or inherit\$) adj3 (cancer\$ or carcinom\$ or neoplasm\$ or tumo?r\$)).ti,ab.
61. (genetic adj2 (screening or test\$)).ti,ab.
62. genogram\$.ti,ab.
63. or/55-62
64. prevention/ or primary prevention/ or prophylaxis/ or breast care/ or cancer prevention/ or chemoprophylaxis/ or periodic medical examination/ or personal monitoring/ or secondary prevention/
65. screening/ or screening test/ or mass screening/ or cancer screening/ or genetic screening/
66. risk/ or genetic risk/ or risk assessment/ or risk factor/ or risk management/ or risk reduction/
67. preventive medicine/
68. preventive health service/
69. prevention.ti.
70. prophylactic.ti.
71. or/64-70
72. (note or comment or editorial).pt.
73. practice guideline/
74. guideline?.ti.
75. 73 or 74
76. 48 and 63 and 75

- 77. 54 and 71 and 75
- 78. 76 or 77
- 79. 78 not 72
- 80. limit 79 to human
- 81. limit 80 to english language
- 82. limit 81 to yr="2003 - 2008"
- 83. 45 or 82

Ovid-CINAHL

- 1. claus.tw.
- 2. gail.tw.
- 3. BRCAPRO.tw.
- 4. BOADICEA.tw.
- 5. UK cancer family study group.tw.
- 6. UKCFSG.tw.
- 7. Myriad.ti,ab.
- 8. tyrer Cuzick.ti,ab.
- 9. ((Amsterdam or Bethesda or Manchester or Gilpin or Evans or Frank or Finnish or Yale or Spanish) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
- 10. FHAT.ti,ab.
- 11. (Australia adj5 breast cancer cent\$).tw.
- 12. couch.ti,ab.
- 13. ((mendel or LAMBDA) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
- 14. (Dutch guideline adj7 breast).ti,ab.
- 15. (nice guideline? and breast cancer).ti,ab.
- 16. or/1-15
- 17. practice guidelines.pt.
- 18. Practice Guidelines/
- 19. guidelines.ti,ab.
- 20. or/17-19
- 21. exp Medical History Taking/
- 22. exp Family Health/
- 23. exp Pedigree/
- 24. ((family or familial) adj3 (histor\$ or history-taking or risk\$)).ti,ab.
- 25. anamnesis.ti,ab.
- 26. (human adj2 pedigree).ti,ab.
- 27. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
- 28. ((famil\$ or heredi\$ or inherit\$) adj3 (cancer\$ or carcinom\$ or neoplasm\$ or tumor\$)).ti,ab.
- 29. or/21-28
- 30. exp Breast Neoplasms/
- 31. exp Colorectal Neoplasms/
- 32. exp Ovarian Neoplasms/
- 33. exp Prostatic Neoplasms/
- 34. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumor\$)).ti,ab.

35. or/30-34
36. cancer screening/ or genetic screening/
37. (surveillance or screening).ti.
38. Preventive Health Care/
39. Chemoprevention/
40. Risk Assessment/
41. prophylactic.ti.
42. prevention.ti.
43. (genic adj2 (counsel?ing or test\$ or screen\$)).ti.
44. Genetic Counseling/
45. (risk adj (assessment? or stratification)).ti.
46. or/36-45
47. exp Neoplasms/
48. (neoplasm? or carcinoma? or cancer?).ti.
49. or/47-48
50. 20 and 29 and 49
51. 20 and 35 and 46
52. 50 or 51
53. limit 52 to (book chapter or case study or commentary or editorial)
54. 52 not 53
55. limit 54 to english
56. limit 55 to yr="2000 - 2008"
57. limit 55 to yr="2003 - 2008"
58. models, theoretical/ or models, statistical/
59. Genes, BRCA/
60. BRCA\$.tw.
61. 59 or 60
62. 58 and 61
63. 16 or 62
64. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
65. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
66. 64 or 65
67. 63 and 66
68. limit 67 to english
69. (book chapter or case study or commentary or editorial).pt.
70. 68 not 69
71. limit 70 to yr="1990 - 2008"
72. 57 or 71

Ovid-CCRT

1. claus.tw.
2. gail.tw.
3. BRCA\$.tw.
4. BOADICEA.tw.

5. UK cancer family study group.tw.
6. UKCFSG.tw.
7. Myriad.ti,ab.
8. tyrer Cuzick.ti,ab.
9. ((Amsterdam or Bethesda or Manchester or Gilpin or Evans or Frank or Finnish or Yale or Spanish) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
10. FHAT.ti,ab.
11. (Australia adj5 breast cancer cent\$).tw.
12. couch.ti,ab.
13. ((mendel or LAMBDA) adj5 (criteria or guideline? or scor\$ or model? or protocol? or algorithm?)).ti,ab.
14. (Dutch guideline adj7 breast).ti,ab.
15. (nice guideline? and breast cancer).ti,ab.
16. or/1-15
17. models, statistical/
18. models, theoretical/ or models, genetic/
19. 17 or 18
20. genes, brca1/ or genes, brca2/
21. BRCA\$.tw.
22. 20 or 21
23. 19 and 22
24. 16 or 23
25. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
26. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
27. *Neoplasms/
28. or/25-27
29. validation.ti.
30. accuracy.ti.
31. validation studies/
32. evaluation studies/
33. exp "Sensitivity and Specificity"/
34. "reproducibility of results"/
35. odds ratio/
36. multivariate analysis/
37. exp Probability/
38. predictive value?.ti,ab.
39. or/29-38
40. 24 and 28 and 39
41. limit 40 to yr="1990 - 2008"
42. Breast Neoplasms/
43. exp Colorectal Neoplasms/
44. exp Prostatic Neoplasms/
45. exp Ovarian Neoplasms/

46. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
47. or/42-46
48. exp Mass Screening/
49. (surveillance or screening).ti.
50. Primary Prevention/
51. Preventive Medicine/
52. prophylactic.ti.
53. prevention.ti.
54. (genetic adj2 (counsel?ing or test\$)).ti.
55. Risk Assessment/
56. (risk adj (assessment? or stratification)).ti.
57. Preventive Health Services/
58. or/48-57
59. exp Pedigree/
60. limit 59 to humans
61. exp Medical History Taking/
62. ((family or familial) adj3 (histor\$ or history-taking or risk\$)).ti,ab.
63. anamnesis.ti.
64. (human adj2 pedigree).ti,ab.
65. (genetic adj2 (risk adj3 (assessment or evaluation))).ti,ab.
66. genogram\$.ti,ab.
67. ((famil\$ or heredi\$ or inherit\$) adj3 (cancer\$ or carcinom\$ or neoplasm\$)).ti,ab.
68. (genetic adj2 (screening or test\$)).ti,ab.
69. Family Health/
70. or/60-69
71. exp Neoplasms/
72. (neoplasm? or carcinoma? or cancer?).ti.
73. 71 or 72
74. guideline.pt.
75. practice guideline.pt.
76. guideline?.ti.
77. or/74-76
78. 70 and 73 and 77
79. 47 and 58 and 77
80. 78 or 79
81. (note or comment or editorial).pt.
82. 80 not 81
83. limit 82 to yr="2003 - 2008"
84. 41 or 83

Question 2

Ovid-MEDLINE

1. exp Diet Therapy/ or exp Nutrition Physiology/ or exp Nutritional Sciences/
2. (diet or diets or dietetic or dietary or eating or intake or nutrient\$ or nutrition or vegetarian\$ or vegan\$ or "seventh day adventist" or macrobiotic or breastfeed\$ or breast feed\$ or breastfed or breast fed or breastmilk or breast milk).ti,ab.
3. exp "food and beverages"/
4. (food\$ or cereal\$ or grain\$ or granary or wholegrain or wholewheat or roots or plantain\$ or tuber or tubers or vegetable\$ or fruit\$ or pulses or beans or lentils or chickpeas or legume\$ or soy or soya or nut or nuts or peanut\$ or groundnut\$ or seeds or meat or beef or pork or lamb or poultry or chicken or turkey or duck or fish or fat or fats or fatty or egg or eggs or bread or oils or shellfish or seafood or sugar or syrup or dairy or milk or herbs or spices or chilli or chillis or pepper\$ or condiments).ti,ab.
5. (fluid intake or water or drinks or drinking or tea or coffee or caffeine or juice or beer or spirits or liquor or wine or alcohol or alcoholic or beverage\$ or ethanol or yerba mate or ilex paraguariensis).ti,ab.
6. fertilizers/ or exp pesticides/ or Veterinary Drugs/
7. (pesticide\$ or herbicide\$ or DDT or fertiliser\$ or fertilizer\$ or organic or contaminants or contaminate\$ or veterinary drug\$ or polychlorinated dibenzofuran\$ or PCDF\$ or polychlorinated dibenzodioxin\$ or PCDD\$ or polychlorinated biphenyl\$ or PCB\$ or cadmium or arsenic or chlorinated hydrocarbon\$ or microbial contamination\$).ti,ab.
8. exp Food Preservation/
9. (mycotoxin\$ or aflatoxin\$ or pickled or bottled or bottling or canned or canning or vacuum pack\$ or refrigerate\$ or refrigeration or cured or smoked or preserved or preservatives or nitrosamine or hydrogenation or fortified or additive\$ or colouring\$ or coloring\$ or flavouring\$ or flavoring\$ or nitrates or nitrites or solvent or solvents or ferment\$ or processed or antioxidant\$ or genetic modif\$ or genetically modif\$ or vinyl chloride or packaging or labelling or phthalates).ti,ab.
10. Cookery/
11. (cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserol\$ or broil or broiled or boiled or microwave or microwaved or re-heating or reheating or heating or re-heated or heated or poach or poached or steamed or barbecue\$ or chargrill\$ or heterocyclic amines or polycyclic aromatic hydrocarbons).ti,ab.
12. exp Dietary Carbohydrates/ or exp Dietary Proteins/ or exp Sweetening Agents/
13. (salt or salting or salted or fiber or fibre or polysaccharide\$ or starch or starchy or carbohydrate\$ or lipid\$ or linoleic acid\$ or sterols or stanols or sugar\$ or sweetener\$ or saccharin\$ or aspartame or acesulfame or cyclamates or maltose or mannitol or sorbitol or sucrose or xylitol or cholesterol or protein or proteins or hydrogenated dietary oils or hydrogenated lard or hydrogenated oils).ti,ab.
14. exp Vitamins/
15. (supplements or supplement or vitamin\$ or retinol or carotenoid\$ or tocopherol or folate\$ or folic acid or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral\$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or allium or

- isothiocyanate\$ or glucosinolate\$ or indoles or polyphenol\$ or phytoestrogen\$ or genistein or saponin\$ or coumarin\$).ti,ab.
16. Physical Fitness/ or exp Exertion/ or exp Physical Endurance/ or Walking/
 17. (recreational activit\$ or household activit\$ or occupational activit\$ or physical activit\$ or physical inactivit\$ or exercise or exercising or energy intake or energy expenditure or energy balance or energy density).ti,ab.
 18. exp Growth/ or exp Anthropometry/ or exp Body Composition/ or exp Body Constitution/
 19. (weight loss or weight gain or anthropometry or birth weight or birthweight or birth-weight or child development or height or body composition or body mass or BMI or obesity or obese or overweight or over-weight or over weight or skinfold measurement\$ or skinfold thickness or DEXA or bio-impedence or waist circumference or hip circumference or waist hip ratio\$).ti,ab.
 20. or/1-19
 21. animals/ not (humans/ and animals/)
 22. 20 not 21
 23. meta-analysis.pt,ti,ab,sh.
 24. (meta anal\$ or metaanal\$).ti,ab,sh.
 25. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti,ab,sh.
 26. (medline or embase or index medicus).ti,ab.
 27. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
 28. 25 or 26 or 27
 29. review.pt,sh.
 30. 28 and 29
 31. 23 or 24
 32. 30 or 31
 33. exp Neoplasms/pc [Prevention & Control]
 34. ((cancer or carcinoma\$ or neoplasm\$) adj3 (prevent\$ or reduc\$)).tw.
 35. Breast Neoplasms/
 36. exp Colorectal Neoplasms/
 37. exp Ovarian Neoplasms/
 38. exp Prostatic Neoplasms/
 39. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
 40. or/33-39
 41. 22 and 32 and 40
 42. limit 41 to english language
 43. limit 42 to ed=20060101-20080425

Ovid-Medline

1. Mass Screening/
2. Smoking Cessation/
3. Alcohol Drinking/
4. Chemoprevention/
5. chemoprevention.ti.
6. (surveillance or screening).ti.
7. Primary Prevention/

8. Preventive Medicine/
9. Preventive Health Services/
10. (prophylactic or preventive or risk reduc\$).ti.
11. risk reduction behavior/
12. "Referral and Consultation"/
13. medical consultation.ti.
14. (health adj3 consultation).ti.
15. or/1-14
16. Breast Neoplasms/
17. exp Colorectal Neoplasms/
18. exp Prostatic Neoplasms/
19. exp Ovarian Neoplasms/
20. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
21. or/16-20
22. self exam\$.ti.
23. Breast Self-Examination/
24. exp Mammography/
25. mammog\$.ti.
26. Ovariectomy/
27. risk reduction mastectomy.ti.
28. ((prophylactic or preventive or risk reduc\$) adj3 (mastectomy or oophorectomy or ovariectomy)).tw.
29. ((magnetic resonance imaging or mri) adj3 breast).ti.
30. breast exam\$.ti.
31. (ovarian adj3 screening).ti.
32. exp Contraceptives, Oral/
33. tamoxifen/ or raloxifene/ or toremifene/
34. (tamoxifen or raloxifene or toremifene or fareston).ti.
35. or/22-34
36. Breast Neoplasms/
37. (breast adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
38. exp Ovarian Neoplasms/
39. (ovar\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
40. or/36-39
41. 35 and 40
42. Fenretinide/
43. Finasteride/
44. (Fenretinide or Finasteride or proscar).ti.
45. Digital Rectal Examination/
46. Toremifene/
47. fareston.ti.
48. (avodart or dutasteride).ti.
49. Prostate-Specific Antigen/
50. (psa adj3 test\$).ti.
51. prostate specific antigen.ti.

52. or/42-51
53. exp Prostatic Neoplasms/
54. (prostat\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
55. or/53-54
56. 52 and 55
57. Digital Rectal Examination/
58. f?ecal occult blood test\$.ti.
59. (FOBT or fob test\$).ti.
60. colonoscopy/ or sigmoidoscopy/
61. (sigmoidoscopy or colonoscopy).ti.
62. Hormone Replacement Therapy/
63. hrt.ti.
64. exp Anti-Inflammatory Agents, Non-Steroidal/
65. NSAID?.ti.
66. (nonsteroidal adj3 inflammatory).ti.
67. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
68. HMG-CoA reductase inhibitors.ti.
69. statins.ti.
70. or/57-69
71. exp Colorectal Neoplasms/
72. ((colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
73. or/71-72
74. 70 and 73
75. genetic services/ or genetic counseling/ or genetic screening/
76. 21 and 75
77. 15 and 21
78. 41 or 56 or 74 or 76 or 77
79. meta-analysis.pt,ti,ab,sh.
80. (meta anal\$ or metaanal\$).ti,ab,sh.
81. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti.
82. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab.
83. (medline or embase or index medicus).ti,ab.
84. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
85. or/82-84
86. review.pt,sh.
87. 85 and 86
88. 79 or 80 or 81 or 87
89. 78 and 88
90. limit 89 to english language
91. limit 90 to yr="2000 - 2008"
92. limit 90 to yr="2003 - 2008"

Ovid-EMBASE

1. exp nutrition/
2. (diet or diets or dietetic or dietary or eating or intake or nutrient\$ or nutrition or vegetarian\$ or vegan\$ or "seventh day adventist" or macrobiotic or breastfeed\$ or breast feed\$ or breastfed or breast fed or breastmilk or breast milk).ti,ab.
3. (food\$ or cereal\$ or grain\$ or granary or wholegrain or wholewheat or roots or plantain\$ or tuber or tubers or vegetable\$ or fruit\$ or pulses or beans or lentils or chickpeas or legume\$ or soy or soya or nut or nuts or peanut\$ or groundnut\$ or seeds or meat or beef or pork or lamb or poultry or chicken or turkey or duck or fish or fat or fats or fatty or egg or eggs or bread or oils or shellfish or seafood or sugar or syrup or dairy or milk or herbs or spices or chilli or chillis or pepper\$ or condiments).ti,ab.
4. (fluid intake or water or drinks or drinking or tea or coffee or caffeine or juice or beer or spirits or liquor or wine or alcohol or alcoholic or beverage\$ or ethanol or yerba mate or ilex paraguariensis).ti,ab.
5. exp Fertilizer/
6. exp Pesticide/
7. Veterinary Drug/
8. (pesticide\$ or herbicide\$ or DDT or fertiliser\$ or fertilizer\$ or organic or contaminants or contaminate\$ or veterinary drug\$ or polychlorinated dibenzofuran\$ or PCDF\$ or polychlorinated dibenzodioxin\$ or PCDD\$ or polychlorinated biphenyl\$ or PCB\$ or cadmium or arsenic or chlorinated hydrocarbon\$ or microbial contamination\$).ti,ab.
9. exp food preservation/
10. (mycotoxin\$ or aflatoxin\$ or pickled or bottled or bottling or canned or canning or vacuum pack\$ or refrigerate\$ or refrigeration or cured or smoked or preserved or preservatives or nitrosamine or hydrogenation or fortified or additive\$ or colouring\$ or coloring\$ or flavouring\$ or flavoring\$ or nitrates or nitrites or solvent or solvents or ferment\$ or processed or antioxidant\$ or genetic modif\$ or genetically modif\$ or vinyl chloride or packaging or labelling or phthalates).ti,ab.
11. cooking/
12. (cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserol\$ or broil or broiled or boiled or microwave or microwaved or re-heating or reheating or heating or re-heated or heated or poach or poached or steamed or barbecue\$ or chargrill\$ or heterocyclic amines or polycyclic aromatic hydrocarbons).ti,ab.
13. *Carbohydrate/
14. exp "peptides and proteins"/ or protein/
15. (salt or salting or salted or fiber or fibre or polysaccharide\$ or starch or starchy or carbohydrate\$ or lipid\$ or linoleic acid\$ or sterols or stanols or sugar\$ or sweetener\$ or saccharin\$ or aspartame or acesulfame or cyclamates or maltose or mannitol or sorbitol or sucrose or xylitol or cholesterol or protein or proteins or hydrogenated dietary oils or hydrogenated lard or hydrogenated oils).ti,ab.
16. exp Vitamin/
17. (supplements or supplement or vitamin\$ or retinol or carotenoid\$ or tocopherol or folate\$ or folic acid or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral\$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or allium or

- isothiocyanate\$ or glucosinolate\$ or indoles or polyphenol\$ or phytoestrogen\$ or genistein or saponin\$ or coumarin\$).ti,ab.
18. exp "physical activity, capacity and performance"/
 19. (recreational activit\$ or household activit\$ or occupational activit\$ or physical activit\$ or physical inactivit\$ or exercise or exercising or energy intake or energy expenditure or energy balance or energy density).ti,ab.
 20. growth/ or exp body growth/
 21. anthropometry/
 22. exp body composition/
 23. body constitution/
 24. (weight loss or weight gain or anthropometry or birth weight or birthweight or birth-weight or child development or height or body composition or body mass or BMI or obesity or obese or overweight or over-weight or over weight or skinfold measurement\$ or skinfold thickness or DEXA or bio-impedence or waist circumference or hip circumference or waist hip ratio\$).ti,ab.
 25. or/1-24
 26. meta-analysis.ti,ab,sh.
 27. (meta anal\$ or metaanal\$).ti,ab,sh.
 28. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti,ab,sh.
 29. (medline or embase or index medicus).ti,ab.
 30. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
 31. 28 or 29 or 30
 32. review.pt,sh.
 33. 31 and 32
 34. 26 or 27 or 33
 35. exp Breast Cancer/
 36. exp Colon Cancer/
 37. exp Ovary Cancer/
 38. exp Prostate Cancer/
 39. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
 40. exp Neoplasm/pc [Prevention]
 41. cancer prevention/
 42. ((cancer or carcinoma\$ or neoplasm\$ or tumo?r\$) adj3 (prevent\$ or reduc\$)).tw.
 43. or/35-42
 44. 25 and 34 and 43
 45. limit 44 to english language
 46. animal/ not (human/ and animal/)
 47. 45 not 46
 48. limit 47 to em=200601-200817

Ovid-EMBASE

1. cancer screening/
2. genetic services/ or genetic counseling/ or genetic screening/
3. prophylaxis/ or breast care/ or cancer prevention/ or chemoprophylaxis/ or periodic medical examination/ or personal monitoring/ or secondary prevention/ or smoking cessation/

4. alcohol abstinence/ or behavioral risk factor surveillance system/ or drinking behavior/ or risk reduction/
5. (chemoprevention or chemoprophylaxis).ti.
6. (surveillance or screening).ti.
7. disease surveillance/
8. PREVENTIVE HEALTH SERVICE/ or PREVENTIVE MEDICINE/
9. (prophylactic or preventive or risk reduc\$).ti.
10. patient referral/
11. medical consultation.ti.
12. (health adj3 consultation).ti.
13. or/1-12
14. exp Breast Cancer/
15. exp Colon Cancer/
16. exp Ovary Cancer/
17. exp Prostate Cancer/
18. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumor\$)).ti,ab.
19. or/14-18
20. exp breast examination/
21. self exam\$.ti.
22. Ovariectomy/
23. exp mastectomy/
24. mammog\$.ti.
25. ((prophylactic or preventive or risk reduc\$) adj3 (mastectomy or oophorectomy or ovariectomy)).tw.
26. ((magnetic resonance imaging or mri) adj3 breast).ti.
27. breast exam\$.ti.
28. (ovarian adj3 screening).ti.
29. exp Oral Contraceptive Agent/
30. raloxifene/ or tamoxifen/ or toremifene/
31. (tamoxifen or raloxifene or toremifene or fareston).ti.
32. or/20-31
33. exp Breast Cancer/
34. (breast adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
35. exp Ovary Cancer/
36. (ovar\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
37. or/33-36
38. 32 and 37
39. Fenretinide/
40. Finasteride/
41. (Fenretinide or Finasteride or proscar).ti.
42. digital rectal examination/
43. Toremifene/
44. fareston.ti.
45. (avodart or dutasteride).ti.
46. Prostate Specific Antigen/

47. (psa adj3 test\$.ti.
48. prostate specific antigen.ti.
49. or/39-48
50. exp Prostate Cancer/
51. (prostat\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
52. or/50-51
53. 49 and 52
54. digital rectal examination/
55. fecal occult blood test\$.ti.
56. (FOBT or fob test\$.ti.
57. colonoscopy/ or sigmoidoscopy/
58. hormone replacement therapy.ti.
59. hrt.ti.
60. exp Hormone Substitution/
61. exp Nonsteroid Antiinflammatory Agent/
62. NSAID?.ti.
63. (nonsteroidal adj3 inflammatory).ti.
64. exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
65. HMG-CoA reductase inhibitors.ti.
66. statins.ti.
67. or/54-66
68. exp Colon Cancer/
69. ((colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
70. or/68-69
71. 67 and 70
72. 13 and 19
73. 38 or 53 or 71 or 72
74. meta analysis/
75. meta-analysis.ti,ab.
76. (meta anal\$ or metaanal\$.ti,ab.
77. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti.
78. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab.
79. (medline or embase or index medicus).ti,ab.
80. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
81. or/78-80
82. review.pt,sh.
83. 81 and 82
84. or/74-77
85. 83 or 84
86. 73 and 85
87. limit 86 to english language
88. limit 87 to yr="2000 - 2008"
89. limit 87 to yr="2003 - 2008"

Ovid-CINAHL

1. Diet Therapy/
2. exp Nutrition/
3. (diet or diets or dietetic or dietary or eating or intake or nutrient\$ or nutrition or vegetarian\$ or vegan\$ or "seventh day adventist" or macrobiotic or breastfeed\$ or breast feed\$ or breastfed or breast fed or breastmilk or breast milk).ti,ab.
4. exp "food and beverages"/ or food/
5. (food\$ or cereal\$ or grain\$ or granary or wholegrain or wholewheat or roots or plantain\$ or tuber or tubers or vegetable\$ or fruit\$ or pulses or beans or lentils or chickpeas or legume\$ or soy or soya or nut or nuts or peanut\$ or groundnut\$ or seeds or meat or beef or pork or lamb or poultry or chicken or turkey or duck or fish or fat or fats or fatty or egg or eggs or bread or oils or shellfish or seafood or sugar or syrup or dairy or milk or herbs or spices or chilli or chillis or pepper\$ or condiments).ti,ab.
6. (fluid intake or water or drinks or drinking or tea or coffee or caffeine or juice or beer or spirits or liquor or wine or alcohol or alcoholic or beverage\$ or ethanol or yerba mate or ilex paraguariensis).ti,ab.
7. exp Pesticides/
8. Veterinary Medicine/
9. (pesticide\$ or herbicide\$ or DDT or fertiliser\$ or fertilizer\$ or organic or contaminants or contaminate\$ or veterinary drug\$ or polychlorinated dibenzofuran\$ or PCDF\$ or polychlorinated dibenzodioxin\$ or PCDD\$ or polychlorinated biphenyl\$ or PCB\$ or cadmium or arsenic or chlorinated hydrocarbon\$ or microbial contamination\$).ti,ab.
10. exp Food Preservation/
11. (mycotoxin\$ or aflatoxin\$ or pickled or bottled or bottling or canned or canning or vacuum pack\$ or refrigerate\$ or refrigeration or cured or smoked or preserved or preservatives or nitrosamine or hydrogenation or fortified or additive\$ or colouring\$ or coloring\$ or flavouring\$ or flavoring\$ or nitrates or nitrites or solvent or solvents or ferment\$ or processed or antioxidant\$ or genetic modif\$ or genetically modif\$ or vinyl chloride or packaging or labelling or phthalates).ti,ab.
12. Cooking/
13. (cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserol\$ or broil or broiled or boiled or microwave or microwaved or re-heating or reheating or heating or re-heated or heated or poach or poached or steamed or barbecue\$ or chargrill\$ or heterocyclic amines or polycyclic aromatic hydrocarbons).ti,ab.
14. exp Dietary Carbohydrates/
15. exp Dietary Proteins/
16. exp Sweetening Agents/
17. (salt or salting or salted or fiber or fibre or polysaccharide\$ or starch or starchy or carbohydrate\$ or lipid\$ or linoleic acid\$ or sterols or stanols or sugar\$ or sweetener\$ or saccharin\$ or aspartame or acesulfame or cyclamates or maltose or mannitol or sorbitol or sucrose or xylitol or cholesterol or protein or proteins or hydrogenated dietary oils or hydrogenated lard or hydrogenated oils).ti,ab.
18. exp Vitamins/
19. (supplements or supplement or vitamin\$ or retinol or carotenoid\$ or tocopherol or folate\$ or folic acid or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral\$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or

- zinc or copper or phosphorus or manganese or chromium or phytochemical or allium or isothiocyanate\$ or glucosinolate\$ or indoles or polyphenol\$ or phytoestrogen\$ or genistein or saponin\$ or coumarin\$).ti,ab.
20. Physical Fitness/
 21. exp Exertion/
 22. Walking/
 23. (recreational activit\$ or household activit\$ or occupational activit\$ or physical activit\$ or physical inactivit\$ or exercise or exercising or energy intake or energy expenditure or energy balance or energy density).ti,ab.
 24. exp Growth/
 25. exp "Body Weights and Measures"/
 26. exp Body Composition/
 27. exp Body Constitution/
 28. (weight loss or weight gain or anthropometry or birth weight or birthweight or birth-weight or child development or height or body composition or body mass or BMI or obesity or obese or overweight or over-weight or over weight or skinfold measurement\$ or skinfold thickness or DEXA or bio-impedence or waist circumference or hip circumference or waist hip ratio\$).ti,ab.
 29. or/1-28
 30. meta-analysis.ti,ab,sh.
 31. (meta anal\$ or metaanal\$).ti,ab,sh.
 32. systematic review.pt.
 33. systematic review.ti.
 34. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti,ab,sh.
 35. (medline or embase or index medicus).ti,ab.
 36. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
 37. 34 or 35 or 36
 38. review.pt,sh.
 39. 37 and 38
 40. 30 or 31 or 32 or 33
 41. 39 or 40
 42. exp Breast Neoplasms/
 43. exp Colorectal Neoplasms/
 44. exp Ovarian Neoplasms/
 45. exp Prostatic Neoplasms/
 46. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
 47. or/42-46
 48. 29 and 41 and 47
 49. limit 48 to ew=2006\$
 50. limit 48 to ew=2007\$
 51. limit 48 to ew=2008\$
 52. 49 or 50 or 51
 53. limit 52 to english

Ovid-CINAHL

1. cancer screening/ or genetic screening/
2. Genetic Counseling/
3. Chemoprevention/
4. "Referral and Consultation"/
5. Smoking Cessation/
6. Alcohol Drinking/
7. (chemoprevention or chemoprophylaxis).ti.
8. Disease Surveillance/
9. (surveillance or screening).ti.
10. Preventive Health Care/
11. (prophylactic or preventive or risk reduc\$).ti.
12. medical consultation.ti.
13. (health adj3 consultation).ti.
14. Risk Management/
15. or/1-14
16. Breast Care/
17. breast examination/ or breast self-examination/
18. self exam\$.ti.
19. Oophorectomy/
20. Mastectomy/
21. Mammography/
22. mammog\$.ti.
23. ((prophylactic or preventive or risk reduc\$) adj3 (mastectomy or oophorectomy or ovariectomy)).tw.
24. ((magnetic resonance imaging or mri) adj3 breast).ti.
25. breast exam\$.ti.
26. (ovarian adj3 screening).ti.
27. exp Contraceptives, Oral/
28. raloxifene/ or tamoxifen/
29. (tamoxifen or raloxifene or toremifene or fareston).ti.
30. or/16-29
31. exp Breast Neoplasms/
32. exp Ovarian Neoplasms/
33. (breast adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
34. (ovar\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
35. or/31-34
36. 30 and 35
37. Finasteride/
38. (Fenretinide or Finasteride or proscar).ti.
39. Digital Rectal Examination/
40. Toremifene.ti.
41. fareston.ti.
42. (avodart or dutasteride).ti.
43. Prostate-Specific Antigen/
44. (psa adj3 test\$).ti.

45. prostate specific antigen.ti.
46. or/37-45
47. exp Prostatic Neoplasms/
48. (prostat\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
49. or/47-48
50. 46 and 49
51. Digital Rectal Examination/
52. fecal occult blood test\$.ti.
53. (FOBT or fob test\$).ti.
54. colonoscopy/ or sigmoidoscopy/
55. Hormone Replacement Therapy/
56. hormone replacement therapy.ti.
57. hrt.ti.
58. exp Antiinflammatory Agents, Non-Steroidal/
59. NSAID?.ti.
60. (nonsteroidal adj3 inflammatory).ti.
61. exp Statins/
62. HMG-CoA reductase inhibitors.ti.
63. statins.ti.
64. or/51-63
65. exp Colorectal Neoplasms/
66. ((colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
67. or/65-66
68. 64 and 67
69. exp Breast Neoplasms/
70. exp Colorectal Neoplasms/
71. exp Prostatic Neoplasms/
72. exp Ovarian Neoplasms/
73. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumor\$)).ti.
74. or/69-73
75. 15 and 74
76. 36 or 50 or 68 or 75
77. Meta Analysis/
78. (meta anal\$ or metaanal\$).ti,ab.
79. meta-analysis.ti,ab.
80. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti.
81. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab.
82. (medline or embase or index medicus).ti,ab.
83. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
84. or/81-83
85. review.pt,sh.
86. 84 and 85
87. "Systematic Review"/
88. systematic review.pt.
89. 78 or 79 or 80 or 86 or 87 or 88

90. 76 and 89
91. limit 90 to english
92. limit 91 to yr="2000 - 2008"
93. limit 91 to yr="2003 - 2008"

Ovid-CDSR

1. (diet or diets or dietetic or dietary or eating or intake or nutrient\$ or nutrition or vegetarian\$ or vegan\$ or "seventh day adventist" or macrobiotic or breastfeed\$ or breast feed\$ or breastfed or breast fed or breastmilk or breast milk).ti,ab.
2. (food\$ or cereal\$ or grain\$ or granary or wholegrain or wholewheat or roots or plantain\$ or tuber or tubers or vegetable\$ or fruit\$ or pulses or beans or lentils or chickpeas or legume\$ or soy or soya or nut or nuts or peanut\$ or groundnut\$ or seeds or meat or beef or pork or lamb or poultry or chicken or turkey or duck or fish or fat or fats or fatty or egg or eggs or bread or oils or shellfish or seafood or sugar or syrup or dairy or milk or herbs or spices or chilli or chillis or pepper\$ or condiments).ti,ab.
3. (fluid intake or water or drinks or drinking or tea or coffee or caffeine or juice or beer or spirits or liquor or wine or alcohol or alcoholic or beverage\$ or ethanol or yerba mate or ilex paraguariensis).ti,ab.
4. (pesticide\$ or herbicide\$ or DDT or fertiliser\$ or fertilizer\$ or organic or contaminants or contaminate\$ or veterinary drug\$ or polychlorinated dibenzofuran\$ or PCDF\$ or polychlorinated dibenzodioxin\$ or PCDD\$ or polychlorinated biphenyl\$ or PCB\$ or cadmium or arsenic or chlorinated hydrocarbon\$ or microbial contamination\$).ti,ab.
5. (mycotoxin\$ or aflatoxin\$ or pickled or bottled or bottling or canned or canning or vacuum pack\$ or refrigerate\$ or refrigeration or cured or smoked or preserved or preservatives or nitrosamine or hydrogenation or fortified or additive\$ or colouring\$ or coloring\$ or flavouring\$ or flavoring\$ or nitrates or nitrites or solvent or solvents or ferment\$ or processed or antioxidant\$ or genetic modif\$ or genetically modif\$ or vinyl chloride or packaging or labelling or phthalates).ti,ab.
6. (cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserol\$ or broil or broiled or boiled or microwave or microwaved or re-heating or reheating or heating or re-heated or heated or poach or poached or steamed or barbecue\$ or chargrill\$ or heterocyclic amines or polycyclic aromatic hydrocarbons).ti,ab.
7. (salt or salting or salted or fiber or fibre or polysaccharide\$ or starch or starchy or carbohydrate\$ or lipid\$ or linoleic acid\$ or sterols or stanols or sugar\$ or sweetener\$ or saccharin\$ or aspartame or acesulfame or cyclamates or maltose or mannitol or sorbitol or sucrose or xylitol or cholesterol or protein or proteins or hydrogenated dietary oils or hydrogenated lard or hydrogenated oils).ti,ab.
8. (supplements or supplement or vitamin\$ or retinol or carotenoid\$ or tocopherol or folate\$ or folic acid or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral\$ or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or allium or isothiocyanate\$ or glucosinolate\$ or indoles or polyphenol\$ or phytoestrogen\$ or genistein or saponin\$ or coumarin\$).ti,ab.
9. (recreational activit\$ or household activit\$ or occupational activit\$ or physical activit\$ or physical inactivit\$ or exercise or exercising or energy intake or energy expenditure or energy balance or energy density).ti,ab.

10. (weight loss or weight gain or anthropometry or birth weight or birthweight or birth-weight or child development or height or body composition or body mass or BMI or obesity or obese or overweight or over-weight or over weight or skinfold measurement\$ or skinfold thickness or DEXA or bio-impedence or waist circumference or hip circumference or waist hip ratio\$.ti,ab.
11. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
12. or/1-10
13. 11 and 12

Ovid-CDSR

1. chemoprevention.ti.
2. (surveillance or screening).ti.
3. (prophylactic or preventive or risk reduc\$.ti.
4. medical consultation.ti.
5. (health adj3 consultation).ti.
6. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
7. self exam\$.ti.
8. mammog\$.ti.
9. risk reduction mastectomy.ti.
10. ((prophylactic or preventive or risk reduc\$) adj3 (mastectomy or oophorectomy or ovariectomy)).tw.
11. ((magnetic resonance imaging or mri) adj3 breast).ti.
12. breast exam\$.ti.
13. (ovarian adj3 screening).ti.
14. (tamoxifen or raloxifene or toremifene or fareston).ti.
15. (breast adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
16. (ovar\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
17. (Fenretinide or Finasteride or proscar).ti.
18. fareston.ti.
19. (avodart or dutasteride).ti.
20. (psa adj3 test\$.ti.
21. prostate specific antigen.ti.
22. (prostat\$ adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti.
23. f?ecal occult blood test\$.ti.
24. (FOBT or fob test\$.ti.
25. hrt.ti.
26. NSAID?.ti.
27. (nonsteroidal adj3 inflammatory).ti.
28. HMG-CoA reductase inhibitors.ti.
29. statins.ti.
30. ((colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$)).ti,ab.
31. or/1-5
32. or/7-14
33. or/15-16

- 34. or/17-21
- 35. or/23-29
- 36. 6 and 31
- 37. 33 and 32
- 38. 22 and 34
- 39. 35 and 30
- 40. or/36-39

Question 3

Ovid-Medline

1. family history.ab.
2. Genetic Predisposition to Disease/
3. BRCA\$.ti.
4. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
5. exp Genetic Services/
6. genes, brca1/ or genes, brca2/
7. or/1-6
8. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
9. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
10. *Neoplasms/
11. or/8-10
12. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (factors or behavio?r\$ or intention or increase or change or impact)).ti.
13. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.
14. ((factors or behavio?r\$ or intention or increase or change or impact or risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.
15. (uptake or motivation or compliance or adherence or seeking or practices or patterns).ti.
16. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (change? or impact? or modification? or influence or risk)).ti.
17. ((after or following or "because of" or "due to" or "result of") adj9 (genetic test\$ or genetic counsel?ing or genetic screening)).ti.
18. ((after or following or "because of" or "due to" or "result of") adj9 (mutation test\$ or mutation screen\$)).ti.
19. exp Health Behavior/
20. risk reduction behavior/
21. or/12-20
22. 7 and 11 and 21
23. animals/ not (humans/ and animals/)
24. 22 not 23
25. limit 24 to english language
26. (note or comment or editorial).pt.
27. 25 not 26
28. limit 27 to yr="1990 - 2008"

Ovid-EMBASE

1. exp health behavior/
2. behavior change/
3. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (factors or behavio?r\$ or intention or increase or change or impact)).ti.
4. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.
5. ((factors or behavio?r\$ or intention or increase or change or impact or risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.
6. (uptake or motivation or compliance or adherence or seeking or practices or patterns).ti.
7. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (change? or impact? or modification? or influence or risk)).ti.
8. ((after or following or "because of" or "due to" or "result of") adj9 (genetic test\$ or genetic counsel?ing or genetic screening)).ti.
9. ((after or following or "because of" or "due to" or "result of") adj9 (mutation test\$ or mutation screen\$)).ti.
10. or/1-9
11. Familial Cancer/
12. exp Breast Cancer/
13. exp Colon Cancer/
14. exp Ovary Cancer/
15. exp Prostate Cancer/
16. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
17. *Cancer/
18. or/11-17
19. genetic predisposition/ or genetic susceptibility/
20. family history/
21. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
22. exp genetic service/
23. brca1 protein/ or brca2 protein/
24. family history.ab.
25. Familial Cancer/
26. BRCA\$.ti.
27. or/19-26
28. 10 and 18 and 27
29. limit 28 to human
30. limit 29 to english language
31. (note or editorial).pt.
32. 30 not 31
33. limit 32 to yr="1990 - 2008"

Ovid-CCRT

1. family history.ab.
2. Genetic Predisposition to Disease/
3. BRCA\$.ti.
4. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
5. exp Genetic Services/
6. genes, brca1/ or genes, brca2/
7. or/1-6
8. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
9. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
10. *Neoplasms/
11. or/8-10
12. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (factors or behavio?r\$ or intention or increase or change or impact)).ti.
13. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.
14. ((factors or behavio?r\$ or intention or increase or change or impact or risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.
15. (uptake or motivation or compliance or adherence or seeking or practices or patterns).ti.
16. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (change? or impact? or modification? or influence or risk)).ti.
17. ((after or following or "because of" or "due to" or "result of") adj9 (genetic test\$ or genetic counsel?ing or genetic screening)).ti.
18. ((after or following or "because of" or "due to" or "result of") adj9 (mutation test\$ or mutation screen\$)).ti.
19. exp Health Behavior/
20. risk reduction behavior/
21. or/12-20
22. 7 and 11 and 21
23. limit 22 to yr="1990 - 2008"

Ovid-CINAHL

1. health behavior/ or patient compliance/ or medication compliance/ or treatment refusal/ or help seeking behavior/
2. Behavioral Changes/
3. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (factors or behavio?r\$ or intention or increase or change or impact)).ti.
4. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utili?ation or "use")).ti.

5. ((factors or behavior?r\$ or intention or increase or change or impact or risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utilization or "use")).ti.
6. (uptake or motivation or compliance or adherence or seeking or practices or patterns).ti.
7. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (change? or impact? or modification? or influence or risk)).ti.
8. ((after or following or "because of" or "due to" or "result of") adj9 (genetic test\$ or genetic counsel?ing or genetic screening)).ti.
9. ((after or following or "because of" or "due to" or "result of") adj9 (mutation test\$ or mutation screen\$)).ti.
10. attitude to change/ or attitude to risk/
11. or/1-10
12. exp Breast Neoplasms/
13. exp Colorectal Neoplasms/
14. exp Ovarian Neoplasms/
15. exp Prostatic Neoplasms/
16. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumor\$)).ti,ab.
17. *Neoplasms/pc [Prevention and Control]
18. or/12-17
19. Genetic Screening/ or Genetic Counseling/
20. Family History/
21. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
22. Genes, BRCA/
23. family history.ab.
24. BRCA\$.ti.
25. or/19-24
26. 11 and 18 and 25
27. limit 26 to english
28. limit 27 to yr="1990 - 2008"

Ovid-PsycINFO

1. health behavior/
2. lifestyle changes/ or behavior change/ or health promotion/ or readiness to change/
3. preventive medicine/ or health promotion/
4. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (factors or behavior?r\$ or intention or increase or change or impact)).ti.
5. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utilization or "use")).ti.
6. ((factors or behavior?r\$ or intention or increase or change or impact or risk) adj8 (mammography or test\$ or screen\$ or exercise or physical activity or diet or food or smoking or alcohol or utilization or "use")).ti.
7. (uptake or motivation or compliance or adherence or seeking or practices or patterns).ti.

8. ((relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk) adj8 (change? or impact? or modification? or influence or risk)).ti.
9. ((after or following or "because of" or "due to" or "result of") adj9 (genetic test\$ or genetic counsel?ing or genetic screening)).ti.
10. ((after or following or "because of" or "due to" or "result of") adj9 (mutation test\$ or mutation screen\$)).ti.
11. risk management/
12. or/1-11
13. at risk populations/ or predisposition/ or "susceptibility (disorders)"/
14. family history.ab.
15. genetics/ or mutations/
16. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
17. genetic testing/ or genetic counseling/
18. BRCA\$.ti.
19. or/13-18
20. breast neoplasms/
21. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
22. *neoplasms/
23. or/20-22
24. 12 and 19 and 23
25. limit 24 to human
26. limit 25 to english language
27. limit 26 to yr="1990 - 2008"

Question 4

Ovid-MEDLINE

1. family history.ab.
2. Genetic Predisposition to Disease/
3. BRCA\$.ti.
4. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
5. exp Genetic Services/
6. genes, brca1/ or genes, brca2/
7. or/1-6
8. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
9. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
10. *Neoplasms/
11. or/8-10
12. anxiety/ or fear/
13. depression/ or stress, psychological/
14. ((worry or anxiety or depression or distress or coping or fear) and cancer).ti.
15. ((psychological or psychosocial) and cancer).ti.
16. (perception and cancer).ti.
17. (impact and cancer).ti.
18. family relations/
19. ((insurance or employment) and cancer).ti.
20. insurance/ or exp insurance, health/
21. insurance.ti.
22. (prejudice or discrimination).ti.
23. (harm? or fatalism).tw.
24. or/12-23
25. employment/ or workplace/
26. prejudice/
27. 24 or 26
28. 7 and 11 and 27
29. animals/ not (humans/ and animals/)
30. 28 not 29
31. (note or comment or editorial).pt.
32. 30 not 31
33. limit 32 to english language
34. limit 33 to yr="1990 - 2008"

Ovid-EMBASE

1. emotional stress/ or family stress/ or interpersonal stress/
2. fear/ or anxiety/
3. exp Depression/
4. ((worry or anxiety or depression or distress or coping or fear) and cancer).ti.

5. ((psychological or psychosocial) and cancer).ti.
6. (perception and cancer).ti.
7. (impact and cancer).ti.
8. family relation/
9. family stress/
10. CANCER FAMILY/
11. ((insurance or employment) and cancer).ti.
12. exp health insurance/
13. insurance/ or exp insurance, health/
14. (prejudice or discrimination).ti.
15. (harm? or fatalism).tw.
16. employment discrimination/
17. or/2-16
18. Familial Cancer/
19. exp Breast Cancer/
20. exp Colon Cancer/
21. exp Ovary Cancer/
22. exp Prostate Cancer/
23. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
24. *Cancer/
25. or/18-24
26. genetic predisposition/ or genetic susceptibility/
27. family history/
28. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
29. exp genetic service/
30. brca1 protein/ or brca2 protein/
31. family history.ab.
32. Familial Cancer/
33. BRCA\$.ti.
34. or/26-33
35. 17 and 25 and 34
36. limit 35 to human
37. (note or comment or editorial).pt.
38. 36 not 37
39. limit 38 to english language
40. limit 39 to yr="1990 - 2008"

OID-CCRT

1. family history.ab.
2. Genetic Predisposition to Disease/
3. BRCA\$.ti.
4. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
5. exp Genetic Services/

6. genes, brca1/ or genes, brca2/
7. or/1-6
8. exp breast neoplasms/ or exp colorectal neoplasms/ or exp ovarian neoplasms/ or exp prostatic neoplasms/
9. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
10. *Neoplasms/
11. or/8-10
12. anxiety/ or fear/
13. depression/ or stress, psychological/
14. ((worry or anxiety or depression or distress or coping or fear) and cancer).ti.
15. ((psychological or psychosocial) and cancer).ti.
16. (perception and cancer).ti.
17. (impact and cancer).ti.
18. family relations/
19. ((insurance or employment) and cancer).ti.
20. insurance/ or exp insurance, health/
21. insurance.ti.
22. (prejudice or discrimination).ti.
23. (harm? or fatalism).tw.
24. or/12-23
25. employment/ or workplace/
26. prejudice/
27. 24 or 26
28. 7 and 11 and 27
29. limit 28 to yr="1990 - 2008"

Ovid-CINAHL

1. exp Breast Neoplasms/
2. exp Colorectal Neoplasms/
3. exp Ovarian Neoplasms/
4. exp Prostatic Neoplasms/
5. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
6. *Neoplasms/pc [Prevention and Control]
7. or/1-6
8. Genetic Screening/ or Genetic Counseling/
9. Family History/
10. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
11. Genes, BRCA/
12. family history.ab.
13. BRCA\$.ti.
14. or/8-13
15. exp Coping/
16. exp "Psychosocial Aspects of Illness"/

17. stress/ or stress, psychological/
18. anxiety/ or depression/
19. Fear/
20. ((worry or anxiety or depression or distress or coping or fear) and cancer).ti.
21. ((psychological or psychosocial) and cancer).ti.
22. (perception and cancer).ti.
23. (impact and cancer).ti.
24. family functioning/ or family coping/ or family relations/
25. ((insurance or employment) and cancer).ti.
26. insurance coverage/ or insurance, health/
27. Discrimination, Employment/
28. (prejudice or discrimination).ti.
29. (harm? or fatalism).tw.
30. or/15-29
31. 7 and 14 and 30
32. limit 31 to english
33. limit 32 to yr="1990 - 2008"

Ovid-PsycINFO

1. coping behavior/ or hopelessness/
2. anxiety/
3. psychological stress/
4. emotional states/ or "depression (emotion)"/
5. fear/
6. ((worry or anxiety or depression or distress or coping or fear) and cancer).ti.
7. ((psychological or psychosocial) and cancer).ti.
8. (perception and cancer).ti.
9. (impact and cancer).ti.
10. distress/
11. family relations/ or interpersonal relationships/
12. emotional adjustment/ or coping behavior/
13. emotional adjustment/
14. or/1-13
15. at risk populations/ or predisposition/ or "susceptibility (disorders)"/
16. family history.ab.
17. genetics/ or mutations/
18. (relative? or genetic or heredit\$ or famil\$ or inherit\$ or high\$ risk or "at risk" or increased risk).ti.
19. genetic testing/ or genetic counseling/
20. BRCA\$.ti.
21. or/15-20
22. breast neoplasms/
23. ((breast or ovar\$ or prostate or colon or colorectal) adj3 (cancer\$ or neoplasm\$ or carcinom\$ or tumo?r\$)).ti,ab.
24. *neoplasms/
25. or/22-24

26. 14 and 21 and 25
27. limit 26 to human
28. limit 27 to english language
29. limit 28 to yr="1990 - 2008"

Appendix B – Forms and Guides

Level 1 – Title and Abstract Screening

Family History II, Screening level 1

1. Is this article non-English or a commentary, editorial or non-systematic review?

Yes (Stop)

No (Continue)

2. Does the citation include any of the following cancers?

Breast/Colorectal/Colon/Rectal/Ovarian/Prostate/Cancer in general (Continue)

None of the above (Stop)

3. Is this a clinical practice guideline?

Yes (Stop)

No (Continue)

4. Is this a systematic review or meta-analysis?

Not a systematic review or meta-analysis (Continue)

A systematic review or meta-analysis that focuses on an intervention to prevent or reduce the risk of cancer? (Stop)

A systematic review or meta-analysis that focuses on family history? (Stop)

A systematic review or meta-analysis on another topic? (Stop)

5. Is this a primary study?

No (Stop)

Yes/Can't Tell (Continue)

6. Is there a reason to believe the citation **FOCUSES** on one or more of the following 3

topics: Risk assessment model /risk stratification/risk algorithm **OR** awareness of cancer family history and uptake of preventative measures and/or health behavior **OR** harms or risks for individuals as a result of having their cancer family history taken.

Yes (Include)

No (Exclude)

Level 2 – Title and Abstract Screening

Family History II, Screening level 2

1. Is this a cancer clinical practice guideline/recommendation?

- Not a clinical practice guideline/recommendation (continue)
- A clinical practice guideline focus on diagnostic screening techniques (stop)
- A clinical practice guideline focus on therapeutic agents (stop)
- A clinical practice guideline focus on surgical procedure (stop)
- clinical practice guideline focus on genetic testing (stop)
- It is a clinical practice guideline/recommendation on another topic. (stop)

2. Is this article a Systematic Review?

- Not a systematic review (Continue)
- A systematic review on behaviors and/or clinical preventive services to change/prevent persons risk for cancer? (Stop)
- It is a non-systematic review.(Stop)
- A systematic review on another topic? (Stop)

3.

Is this a citation focused on one of the following topics:

- Risk assessment model /risk stratification/risk algorithm
- Is this about uptaking preventative measures and/or behavior change and/or clinical preventive services?
- Is this about harm/risk of collection of family history or provision of family history based risk information?
- Is this about harms/risk of genetic testing and/or genetic counseling?
- No (exclude)

Level 3 – Full Text Screening - Phase I

Family History II, Screening level 3

1. Does this citation include the following cancers? (Check all that apply)

- Breast
- Ovarian
- Prostate
- Colorectal/colon/Rectal
- Cancer in general
- None of the above (exclude)

2. Does this citation describe guidelines/recommendations on diagnoses including risk assessment or risk stratification?

- Yes (stop)
- No (continue))
- Other guideline (stop)

3. Is this a Systematic Review?

- Yes (continue)
- No (GO to Q6)

4. Is this a systematic review on behaviors and /or clinical preventive services to change/reduce a person's risk for cancer?

- Yes (continue)
- No(stop)

5. Is this article a Systematic Review on food, nutrition, physical activity, obesity, smoking, alcohol, and the prevention on cancer* published before 2006? (*see the list)

- Yes (stop)
- No (stop)

6. What type of primary study is this citation?

- Cohort
- Case Control
- Experimental
- Others

■ It is not a primary study (stop)

7. Does this article describe risk prediction equations/mathematical models OR risk stratification algorithms OR Risk assessment model?

Yes (continue)

No (Go to Q9)

8. Is the model based substantially on family history information?

Yes (stop)

No(stop)

9. Is this article about the uptake of behaviours or clinical preventive services to reduce risk of cancer?

Yes (continue)

No (go to Q11)

10. Does this article mention subjects have been informed of personal risk of breast, colorectal, prostate and/or ovarian cancer based on family history or at least had their family history taken?

Yes (stop)

No (stop)

11. Is this article about harm/injury/increased risk for individuals as a result of having their cancer family history taken or the provision of family history based risk information?

Yes

No

12. Is this a dissertation, conference abstract, workshop proceeding, or an old guideline?

Yes (exclude)

Level 4 – Full Text Screening – Phase II

Family History II, Screening level 4 (Q1234G)

1. what question does this citation answer?

- Q1 (Go to Q2---5, Blue color)
- Q2 (Go to Q6---8, -Green color)
- Q3 (Go to Q9 ---13, -Red color)
- Q4 (Go to Q14---16, Purple color)
- Guideline (Go to Q17---20, Brown color)
- none of the above

2. Is the risk/algorithm designed to predict or categorize/stratify risk of cancer or risk of a cancer mutation? *(Note that a model/ algorithm that focuses on treatment alone, should not be included. If the model/ algorithm also provides information on follow-up after the intervention (for example, surgery, or other treatments) that includes actions or recommendations based on family history)*

- Yes
- No (stop)

3. Is the risk/ algorithm system designed to stratify people into ≥ 2 risk categories OR provide a numerical point estimate or risk?

- Yes
- No
(exclude)

Not sure

4. Does this study undertake validation on a sample that is unselected (for risk of cancer) and representative of a primary care sample?

- Yes
- No (specify reason)
- Not sure (specify reason)

5. Reviewer comments:

6.

For SR what type of study designs are included in its eligibility criteria?

- Randomized Controlled Trials (RCT)

- Non-randomized controlled trials
- Uncontrolled trials (before-after)
- SR but None of the above
- Can not tell
- not a SR

7. Is the intervention in this review one that is relevant for research question 2 (see list)?

- Yes
- No (stop)
- Not sure

8.

Does this paper have the appropriate Outcomes AND unselected POPULATION:

- Yes
- Not sure
- No (specify reason)

9. Does the POPULATION of this study include?

- General unselected population
- Primary care patients who are unselected
- Persons who are participating in a general screening program
- People with high risk of cancer, as estimated by an existing risk assessment system or a genetics specialist OR Populations sampled from specialist genetics clinics or cancer family clinics OR People who have had a genetic test for a mutation related to one of the cancers of interest OR Persons who have cancer (exclude if any of the above criteria are met)

10. What is the STUDY DESIGN for this citation?

- Randomized Clinical Trial
- Non-randomized Clinical Trial
- Before After-study
- Other (exclude)

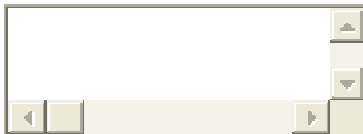
11. Does the study include the systematic provision of personal risk of breast, colorectal, prostate and/or ovarian cancer based on FAMILY HISTORY? (WITH OR WITHOUT Individual advice on appropriate risk reduction behaviors and/or services (where recommended behavior or service was considered standard of care at the time of the study))

- Yes (continue)
- No (exclude)
- Can't tell

12. Does this citation also address research Q4?

- Yes
- No
- Not sure

13. Reviewer comments:



14. What is the study design of this citation?

- Randomized Clinical Trial
- Non-randomized Clinical Trial
- Before After-study
- Other (continue to next question))

15. Does the POPULATION of this study include?

- General unselected population.
- Primary care patients who are unselected
- Persons who are participating in a general screening program
- People with high risk of cancer, as estimated by an existing risk assessment system or a genetics specialist OR Populations sampled from specialist genetics clinics or cancer family clinics OR People who have had a genetic test for a mutation related to one of the cancers of interest OR Persons who have cancer (exclude if any of the above criteria are met)

16. Does this paper have the appropriate Outcomes?

- Yes
- Not sure (specify)
- No (specify reason)

17. Is one of the aims of the guideline designed to predict or categorize/stratify risk of cancer or risk of a cancer mutation AND does the guideline include a family history component?

(Note that some guidelines have multiple components (treatment, screening, management) and there must be an explicit indication of collecting cancer family history).

Yes

No

(stop)

Not sure

18. Is the guideline system designed to stratify people into greater than or equal to 2 risk categories OR provide a numerical point estimate or risk?

Yes

No

(exclude)

Not sure

19. Does this guideline delineate information about the accuracy or validity of the guideline? The accuracy can be expressed as diagnostic accuracy (sensitivity, specificity, positive predictive values, etc) for either predicting cancer or cancer mutation.

Yes

No (specify reason)

Not sure (specify reason)

20. Reviewer comments:

Family History II, Screening level 1- Guidelines

1. Is this article non-English or a commentary, editorial or NON-systematic review?

- Yes (Stop)
- No (Continue)

Instruction:

If the citation is in a language other than English, is a commentary or editorial or is a non-systematic review (i.e. a review that is not systematic) you should answer "YES" and then go on to the next citation (don't forget to click "submit" or your answers won't be recorded).

If the citation is for a PRIMARY study, a clinical practice guideline or a systematic review (or any study type not listed above) you should answer "NO" and then continue screening

2. Does the citation include any one of the following cancers?

- Breast/Colorectal/Colon/ Rectal/Ovarian/Prostate/Cancer in general (Continue)
- None of the above (Stop)

Instruction:

Question 2: We are only interested in studies about Breast, Ovarian, Prostate and Colorectal Cancers. If the study does not specify the type of cancer, choose "cancer in general"

3. Is this a cancer clinical practice guideline?

- Yes (Stop)
- No (Continue)

4. Is this article a Systematic Review?

- Not a systematic review (Continue)
- A systematic review on an intervention to PREVENT, reduce the risk of cancer? (Stop)
- A systematic review about family history? (Stop)
- A systematic review on another topic? (Stop)

Instruction 1 for Question 4:

Please note that the word INTERVENTION is used in the generic sense to indicate a lifestyle or service obtained that will result in a **CHANGE** in a person's risk for cancer. This change can be **positive or negative** (e.g. alcohol consumption is associated with an increased risk of some cancers). The review does NOT have to show that the lifestyle change or preventive service **CAUSES** change in cancer risk, only that it is **ASSOCIATED** with a change in risk.

That means that for both citation A and B below you should choose would choose “A systematic review or meta-analysis that focuses on an intervention to prevent or reduce the risk of cancer?”

- A. Low fat eating pattern intervention and risk of colorectal cancer in postmenopausal women: a systematic review
- B. Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: a meta-analysis

Instruction 2 for Question 4:

Look carefully for words like “systematic review”, “meta analysis”, “Cochrane review” or “pooling”, or some description of the methods used to assemble papers:

- sort of detailed search info such as describes methods for searching 1 or more databases (MEDLINE, etc)
- discusses inclusion and exclusion criteria

NB:

- This can include people who have had cancer and are taking steps to avoid a **RECURRENCE**
- Exclude if the intervention is **CLEARLY USED ONLY** to **TREAT/ MANAGE** cancer patients rather than **PREVENT** recurrences.
- For example, if radiation therapy or drugs are being used in patients with cancer, it is likely that this study is focused on **TREATING** patients with cancer, not preventing cancer or **RECURRENCES**.

Examples of common interventions to PREVENT or reduce the risk of cancer (list is partial, include any intervention that you find)

Breast:

Specific behaviors:

- breast self-examination

Specific clinical preventive services:

- annual clinical examination
- mammography
- clinical breast examination
- cancer chemoprevention
- magnetic resonance imaging breast screening (MRI)
- genetic counseling +/- genetic testing
- risk-reduction mastectomy/oophorectomy (RRM/O)

Colorectal:

Specific clinical preventive services:

- Screening/surveillance activities

- FOB test
- sigmoidoscopy
- digital rectal exam
- colonoscopy
- genetic counseling +/- genetic testing

Ovarian:

Specific clinical preventive services:

- genetic counseling +/- genetic testing
- prophylactic oophorectomy
- ovarian screening
- genetic counseling +/- genetic testing

Prostate:

Specific clinical preventive services:

- Screening/surveillance activities:
 - PSA test
 - digital rectal examination
- chemoprevention
- genetic counseling +/- genetic testing

General behaviors for all four cancers:

- regular exercise/physical activity
- high fiber diet
- increased fruit and vegetable consumption
- low fat diet
- smoking cessation
- reduction in alcohol intake
- seeking health care advice

5. Is this a Primary Study?

- No (Stop)
- Yes (Continue)
- Can't Tell (Continue)

•

6. Is there a reason to believe the citation FOCUSES on one or more of the following 3 topics: Risk assessment model /risk stratification/risk algorithm **OR** awareness of cancer family history and uptake of preventative measures and/or health behavior **OR** harms or risks for individuals as a result of having their cancer family history taken.

- Yes (Include)

No (Exclude)

Instruction: question 6.

We are including primary studies that focus on one or more of the 3 following topics:

1. Some risk assessment model /risk stratification/risk algorithm tools are listed below. Note this is only a partial list; include any you find that you think are risk assessment tools.

- Gail
- Claus
- Tyrer-Cuzick
- Couch
- BRCA-PRO
- UK Cancer Family Study Group
- BOADICEA
- French National agency for health evaluation
- National Breast Cancer Centre (Australia)
- Amsterdam and modified Amsterdam
- Scottish Cancer Group
- MYRIAD (Frank)
- Bethesda
- Manchester
- USPSTF
- FHAT
- Jonker
- Ontario Stratification algorithm

Definition of Risk Assessment tools (models or algorithm)

Models that stratify risk use several different pieces of information. Based on this information patients are categorized into high, medium or low risk for either getting cancer or having a high risk gene (mutation). A tool/ model/ algorithm usually has a name (see provided list) and is almost always used by physicians

2. Awareness of cancer family history and uptake of preventative measures and/or health behaviors

- Include if the abstract states that based on the participants knowing their cancer family history, are evaluated for their uptake of specific actions. These generally include either behavioral changes (e.g. changes in diet or activity level, self-exam) or clinical preventive services (e.g., chemoprevention, prophylactic surgery, screening,).
- Exclude if it is **CLEARLY** an intervention **ONLY** to improve the outcome for those **WITH** cancer. For example, a mastectomy that is not prophylactic (preventing the cancer from occurring) but is being undertaken to **TREAT** the cancer. This should be excluded as it is not showing that the preventative measure (i.e. mastectomy) was not undertaken to prevent cancer. Be careful as interventions like Tamoxifen as a treatment versus its use as a prevention measure. We are interested in it with regards to prevention.

- If there is any doubt includes the abstract OR send us a message with your queries.

3. Harms or risks for individuals as a result of having their cancer family history taken.

Examples of HARMS include:

- Psychological impacts like fear, depression, anxiety, family function impacts, discrimination in employment or insurance, fatalism, health problems, quality of life issues, deciding not to have children because of FH
- Behaviour changes due to perception or misperception of risk (i.e. fatalism or thinking you are low risk) examples: someone starts eating a high fat diet or quits exercising because they think they are going to get cancer anyway or because they believe that they aren't at risk.

Exclude articles that

- Focus on the negative impacts of HAVING cancer (there will be quite a few of these). So if spouse leaves because their partner HAS cancer, exclude.
- BUT if they leave because they learned that their partner has a family history of cancer (increased risk real or perceived), include it. If the distinction is unclear err on the side of caution and include it.
- Exclude articles if the harm is clearly secondary for example, if a person has a prophylactic mastectomy because of their family history and has surgical complications. If the distinction is unclear err on the side of caution and include it.
- Any harms that result from having undertaken a preventive measure, like a prophylactic mastectomy followed by surgical complications, should be excluded.

Appendix C – Eligible Studies Extracted and Those Retained But Not Extracted

Table 1. Eligible Studies Extracted and Those Retained But Not Extracted

Retained But Not Extracted	<i>Superseded by (extracted)</i>
Huang 2006 ¹ Huang 2006 ²	Bardia 2008 ³
Moayyedi 2006 ⁴	Hewitson 2007 ⁵
Walsh 2003 ⁶	Hewitson 2007 ⁵
Bonovas 2007 ⁷ Bonovas 2005 ⁸	Browning 2007 ⁹
Hoffmeister 2006 ¹⁰	Dubé 2007 ¹¹
Asano 2004 ¹²	Dubé 2007 ¹¹
Coulter 2006 ¹³	Alkhenizan 2007 ¹⁴
Dale 2006 ¹⁵	Browning 2007 ⁹
Heresbach 2006 ¹⁶	Hewitson 2007 ⁵
Hackshaw 2003 ¹⁷	Kosters 2003 ¹⁸
	Gotzsche 2006 ¹⁹
	Kerr 2007 ²⁰
	Bristol SLR Team 2006 ²¹
	Ilic 2006 ²²
Eligible, but did not report usable data	
Dutch Review Team, Bakker 2006 ²³	
Italian Review Team, Agnoli 2005 ²⁴	
Eligible, but no eligible intervention studies identified	
Mahmud 2004 ²⁵	
Rostom 2007 ²⁶	
Weingarten 2008 ²⁷	
Brett 2005 ²⁸	
Watson 2005 ²⁹	

Reference List for Appendix C – Studies Retained But Not Extracted

1. Huang HY, Caballero B, Chang S et al. Multivitamin/mineral supplements and prevention of chronic disease. Evid Rep Technol Assess No.139, AHRQ Publication No.06-E012. (Prepared by The Johns Hopkins University Evidence-based Practice Center under Contract No.290-02-0018). Rockville, MD: Agency for Healthcare Research and Quality; 2006 May. [PM:17764205](#)
2. Huang HY, Caballero B, Chang S, et al. The efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults: a systematic review for a National Institutes of Health state-of-the-science conference. [Review] [44 refs]. *Ann Intern Med* 2006;145(5):372-85.
3. Bardia A, Tleyjeh IM, Cerhan JR, et al. Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. [Review] [73 refs]. *Mayo Clin Proc* 2008;83(1):23-34.
4. Moayyedi P, Achkar E. Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data.[Review] [25 refs]. *Am J Gastroenterol* 2006;101(2):380-4.
5. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult.[update of Cochrane Database Syst Rev. 2000;(2):CD001216; PMID: 10796760]. [Review] [46 refs]. *Cochrane Database Syst Rev* 2007;(1):CD001216
6. Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review.[Review] [105 refs]. *JAMA* 2003;289(10):1288-96.
7. Bonovas S, Filioussi K, Flordellis CS, et al. Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol* 2007;25(23):3462-8.
8. Bonovas S, Filioussi K, Tsavaris N, et al. Use of statins and breast cancer: A meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005;23(34):8606-12.
9. Browning DR, Martin RM. Statins and risk of cancer: A systematic review and metaanalysis. *Int J Cancer* 2007;120(4):833-43.
10. Hoffmeister M, Chang-Claude J, Brenner H. Do older adults using NSAIDs have a reduced risk of colorectal cancer? *Drugs Aging* 2006;23(6):513-23.
11. Dube C, Rostom A, Lewin G, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007;146(5):365-75.
12. Asano TK, McLeod RS. Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: a systematic review. [Review] [45 refs]. *Dis Colon Rectum* 2004;47(5):665-73.
13. Coulter ID, Hardy ML, Morton SC, et al. Antioxidants Vitamin C and Vitamin E for the Prevention and Treatment of Cancer. *J Gen Intern Med* 2006;21(7):735-44.
14. Alkhenizan A, Hafez K. The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials. *Ann Saudi Med* 2007;27(6):409-14.
15. Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. *JAMA* 2006;295(1):74-80.
16. Heresbach D, Manfredi S, D'halluin PN, et al. Review in depth and meta-analysis of controlled trials on colorectal cancer screening by faecal occult blood test. [Review] [61 refs]. *Eur J Gastroenterol Hepatol* 2006;18(4):427-33.
17. Hackshaw AK, Paul EA. Breast self-examination and death from breast cancer: a meta-analysis. *Br J Cancer* 2003;88(7):1047-53.
18. Kusters JP, Gotzsche PC. Regular self-examination or clinical examination for early detection of breast cancer [Review] [24 refs]. *Cochrane Database Syst Rev* 2003;(2):CD003373
19. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2006;(4):CD001877
20. Kerr J, Day P, Broadstock M, et al. Systematic review of the effectiveness of population screening for colorectal cancer. [Review] [28 refs]. *N Z Med J* 2007;120(1258):U2629
21. Bristol SLR Team 2006. Systematic Literature Review Report. The associations between food, nutrition, physical activity and the risk of prostate cancer and underlying mechanisms. World Cancer Research Fund/American Institute for Cancer Research, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: 2006 Jun 30.
22. Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer. *Cochrane Database Syst Rev* 2006; Issue 3, Art.No.: CD004720.DOI:10.1002/14651858.CD004720.pub 2:
23. Dutch Review Team 2006. Systematic Literature Review Report. The associations between food, nutrition and physical activity and the risk of colorectal cancer and underlying mechanisms. World Cancer Research Fund/American Institute for Cancer Research, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: 2007.
24. Italian Review Team 2005. Systematic Literature Review Report. The Associations between Food, Nutrition and Physical Activity and the Risk of Breast Cancer and Underlying Mechanisms. World Cancer Research Fund/American Institute for Cancer Research, Food, Nutrition, Physical

- Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: 2007.
25. Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. [Review] [43 refs]. *Br J Cancer* 2004;90(1):93-9.
 26. Rostom A, Dube C, Lewin G, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007;146(5):376-89.
 27. Weingarten MA, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps.[update of *Cochrane Database Syst Rev*. 2005;(3):CD003548; PMID: 16034903]. [Review] [38 refs]. *Cochrane Database Syst Rev* 2008;(1):CD003548
 28. Brett J, Bankhead C, Henderson B, et al. The psychological impact of mammographic screening. A systematic review. [Review] [74 refs]. *Psychooncology* 2005;14(11):917-38.
 29. Watson EK, Henderson BJ, Brett J, et al. The psychological impact of mammographic screening on women with a family history of breast cancer--a systematic review. [Review] [26 refs]. *Psychooncology* 2005;14(11):939-48.

Appendix D - Excluded Studies

1. Abbadessa G, Santoro A, Claudio PP. 42nd Annual Meeting of the American Society of Clinical Oncology (ASCO) (June 2-6, Atlanta) 2006. *Drugs of the Future* 2006;31(7):617-23. Excluded: Not an eligible study design, OVID-Embase.
2. Abdel-Fattah M, Zaki A, Bassili A, et al. Breast self-examination practice and its impact on breast cancer diagnosis in Alexandria, Egypt. *East Mediterr Health J* 2000;6(1):34-40. Excluded: Family history not systematically collected, OVID-Medline.
3. Absetz P, Aro AR, Sutton SR. Experience with breast cancer, pre-screening perceived susceptibility and the psychological impact of screening. *Psychooncology* 2003;12(4):305-18. Excluded: Family history not systematically collected, OVID-Medline.
4. Abu-Rustum NR, Herbolsheimer H. Breast cancer risk assessment in indigent women at a public hospital. *Gynecol Oncol* 2001;81(2):287-90. Excluded: Model does not categorize risk or validate, OVID-Medline.
5. ACOG: American College of Obstetricians and Gynecologists. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 42, April 2003. Breast cancer screening. *Obst Gynecol* 2003;101(4):821-31. Excluded: Model does not categorize risk or validate, OVID-Medline.
6. ACOG: American College of Obstetricians and Gynecologists. ACOG practice bulletin. Breast cancer screening. Number 42, April 2003. *Int J Gynaecol Obstet* 2003;81(3):313-23. Excluded: Model does not categorize risk or validate, OVID-Medline.
7. ACOG: American College of Obstetricians and Gynecologists. ACOG committee opinion. Routine cancer screening. Number 247, December 2000. *Int J Gynaecol Obstet* 2003;82(2):241-5. Excluded: Model does not categorize risk or validate, OVID-Medline.
8. ACOG: American College of Obstetricians and Gynecologists. ACOG Committee on Gynecologic Practice. Committee opinion no. 356: Routine cancer screening. *Obstet Gynecol* 2006;108(6):1611-3. Excluded: Model does not categorize risk or validate, OVID-Embase.
9. Agrawal A, Fentiman IS. NSAIDs and breast cancer: A possible prevention and treatment strategy. *Int J Clin Pract* 2008;62(3):444-9. Excluded: Not an eligible study design, OVID-Embase.
10. Ahmed NU, Fort JG, Elzey JD, et al. Empowering factors in repeat mammography: insights from the stories of underserved women. *J Ambulatory Care Manage* 2004;27(4):348-55. Excluded: Family history not systematically collected, OVID-Medline.
11. Ahmed NU, Fort JG, Elzey JD, et al. Empowering factors for regular mammography screening in under-served populations: pilot survey results in Tennessee.[see comment]. *Ethn Dis* 2005;15(3):387-94. Excluded: Family history not systematically collected, OVID-Medline.
12. Aiken LS, Fenaughty AM, West SG, et al. Perceived determinants of risk for breast cancer and the relations among objective risk, perceived risk, and screening behavior over time. *Womens Health* 1995;1(1):27-50. Excluded: Family history not systematically collected, OVID-Medline.
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