Systematic Review: Family History in Risk Assessment for Common Diseases

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Background: The usefulness of routinely examining family history in primary care practice is uncertain.

Purpose: To assess the beneficial and adverse effects of collecting family history in primary care populations; how well family history predicts individual disease risk; and how accurately patients report it.

Data Sources: English-language studies in MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, and PsycINFO from 1995 to 2 March 2009.

Study Selection: Two independent reviewers selected studies that met question-specific eligibility criteria. These included controlled and uncontrolled intervention studies of systematic family history collection and uptake of preventive interventions or adverse effects, longitudinal and cross-sectional studies that examined family history and disease frequency, and studies in which reported family history was validated against relatives’ true disease status.

Data Extraction: Information about study quality, setting, and findings was extracted using standardized protocols.

Data Synthesis: Two uncontrolled studies provided insufficient evidence to assess whether querying about family history improves any outcomes. One randomized, controlled trial and 2 uncontrolled studies provided weak evidence that some patients experienced a reversible, short-term increase in anxiety associated with family history taking. In 41 studies, different family history definitions were associated with sensitivities of 0 to 0.51 and specificities of 0.66 to 1.00 for detection of disease risk, and 0 to 0.83 and 0.48 to 1.00, respectively, for detection of prevalent disease. Twenty-three studies suggested that absence of disease in relatives was more accurately reported than presence of disease and that reporting accuracy was higher for information related to first-degree relatives than more distant relatives.

Limitation: Few studies were designed to address the specific questions of interest.

Conclusion: Insufficient evidence evaluates how to collect family history information accurately in the primary care setting and the effects of taking family history on patient outcomes. Patients seem to correctly report the absence of disease in relatives more often than the presence of disease.

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Family history represents the integration of risk within a family from shared genetic susceptibilities and familial clustering of environmental exposures, lifestyles, and behaviors. Epidemiologic evidence shows associations between family history and risk for many common chronic diseases (1–7). Thus, family history information might aid in assessing risk for a condition, even in the absence of an understanding of the molecular cause of that condition and even for disorders that do not follow a distinct Mendelian inheritance pattern. Knowledge of family history might also act as a motivator for behavior change (8).

As with any health care intervention, family history–based risk assessment carries resource implications and opportunity costs. We present evidence about the potential beneficial and harmful effects of collecting and using family history information, family history elements that are most useful for risk assessment, and the accuracy of family history information reported by patients. We focus on family history collection and interpretation in a primary care context, in which the population presents a full range of disease risks, primary care practitioners obtain history information, and chronic disease risk assessment and prevention is the goal.

Methods

We developed and followed a standard protocol for all steps of the review. A technical report that details methods, including the literature search strategies, and presents results for 6 original research questions is available at wwwahrq.gov. The Appendix and Appendix Figure, available at www.annals.org, provide further details of our methods and analytic framework.

Key Questions

This evidence review addresses 4 of 6 original research questions developed by a panel from the National Human
Genome Research Institute and the Office of Medical Applications of Research of the National Institutes of Health. A representative from the panel and the Technical Expert Panel helped refine the scope of the questions and define pertinent eligibility criteria. They recommended focusing on primary care and selecting experimental and quasi-experimental designs for the effectiveness questions.

1. What is the direct evidence that getting a family history will improve health outcomes for the patient or family?
2. What is the direct evidence that getting a family history will result in adverse outcomes for the patient or family?
3. What are the key elements of a family history in a primary care setting for the purposes of risk assessment for common diseases?
4. What is the accuracy of family history, and under what conditions does the accuracy vary?

Data Sources and Selection
We searched for English-language publications in MEDLINE, EMBASE, CINAHL, the Cochrane Central Registry of Controlled Trials, and PsycINFO from 1995 to 2 March 2009. With the exception of question 4, we restricted participants to those who were unselected for high preexisting risk and recruited from general population settings. We excluded studies of patients undergoing genetic testing because of suspicion of high a priori risk. We defined the intervention as the systematic collection of family history by any means, alone or with other risk information. For questions 1 and 2, we restricted study designs to randomized, controlled trials; nonrandomized trials; and before–after studies. For question 3, we restricted designs to retrospective and prospective cohort studies and cross-sectional studies and the conditions of interest to breast, colorectal, ovarian, prostate, and lung cancer; coronary heart disease; stroke; and diabetes. For question 4, we did not restrict study design. The eligible outcomes varied with the research questions. (Full technical report is available at www.ahrq.gov.)

Trained research assistants independently screened each citation using standardized forms and a training manual developed by the reviewers. They assessed eligibility on the basis of title and abstract and retrieved articles if at least 1 judged it potentially eligible. At full-text screening, 2 assistants came to consensus on the identification, selection, and data abstraction. We reviewed all reports with unclear eligibility and resolved any disagreements about selection or data by discussion.

Data Extraction and Quality Assessment
We extracted data on participant characteristics, method of family history collection, study outcomes, study design, and quality. At least 1 reviewer confirmed all data extraction. We assessed quality on the basis of randomization, blinding processes, and completeness of follow-up for controlled trials (9); risk for selection and outcome biases for uncontrolled before–after studies; selection and information biases for longitudinal and cross-sectional analyses relevant to question 3; and spectrum, selection, verification, and masking biases for studies relevant to question 4 (10). For question 4, we treated patient reporting of family history as the index test and the verified disease status of the relatives as the reference test; we assumed that both the index test and the reference test were equivalent across studies.

Data Synthesis and Analysis
We used a descriptive approach to summarize study characteristics and outcomes for all research questions. For question 3, we compared the predictive accuracy of family history elements by first considering specific ancestry, specific relative of interest (for example, mother), degree of relative of interest’s relationship to informant (for example, first degree), age of onset of condition in affected relative, and lineage of affected relative (informant’s maternal or paternal line) to be categories of family history elements. We then treated any definition of positive family history reported in an article as a combination of these elements. For each report, we noted the elements each definition incorporated. We then calculated the sensitivity and specificity of each definition for predicting or detecting the disease of interest, treating fulfillment of the definition as the test and nonfulfillment as the reference. For each condition, we compared the sensitivities and specificities for each definition (each combination of 1 or more elements).

We decided that meta-analysis was inappropriate because of an insufficient number of studies and data for questions 1 and 2; important clinical heterogeneity across studies and nonindependence of many observations for question 3; and important clinical heterogeneity across studies, insufficient studies for some disease categories, and missing measures of variance for evidence relevant to question 4.

Role of the Funding Source
The Agency for Healthcare Research and Quality, in partnership with the National Institutes of Health Office of Medical Applications of Research Consensus Conferences, suggested the initial questions. The Agency for Healthcare Research and Quality provided copyright release for this manuscript. Both the Agency for Healthcare Research and Quality and the National Institutes of Health Office of Medical Applications of Research representatives were informed of key methodological decisions but did not participate in the literature search, data analysis, or interpretation of the results.

RESULTS
We screened 32,444 titles and abstracts and evaluated 1254 full-text articles. A total of 137 publications met eligibility criteria (Appendix Figure). The Table (11–79) summarizes the reviewed studies.
Evidence That Getting a Family History Improves Outcomes

We identified 2 uncontrolled before–after studies (11, 12) that evaluated the effect of collecting family history of breast or ovarian cancer with risk personalization on adherence with recommended breast cancer screening behaviors (Appendix Tables 1 and 2, available at www.annals.org). One study was workplace-based (11), and the other recruited walk-in clients of community pharmacies and health fair participants (12). The intervention was telephone-based in 1 study and in-person in the other. The outcomes for both studies were self-reported rates of breast self-examination, clinical breast examination, and screening mammography at 8 (11) or 6 (12) months.

Both studies showed an increase in breast self-examination rates, from 34% to 62% (11) and 31% to 56% (12), and an increase in clinical breast examination rates, from 82% to 92% (P = 0.014) (11) and 86% to 91% (P < 0.009) (12). One study showed an increase in mammography uptake from 76% to 93% (P < 0.057) (11), and the other showed a decrease from 75% to 70% (P < 0.48) (12).

These 2 studies provide limited and insufficient evidence about the effect of collecting family history and personalizing risk on health behavior. They had low statistical power, lacked control groups, and had concurrent co-interventions—such as awareness campaigns—that probably affected results. Also, study participants were from self-selected groups who had relatively high baseline rates of adherence to screening recommendations.

Evidence That Getting a Family History Causes Harm

We identified 1 randomized, controlled trial (13), with 100 randomly assigned and 76 analyzed participants, and 2 uncontrolled before–after studies (14, 15) (Appendix Tables 3 and 4, available at www.annals.org). Two studies (13, 15) evaluated generic family history assessment, and 1 (14) specifically evaluated cancer history assessment. One study evaluated family history as part of a periodic health examination (13), the second within a dedicated family practice clinic (15), and the third through a special postal survey (14). Personalized risk was provided in person in 2 studies (13, 15) and by letter (low-risk respondents) or in person (high-risk respondents) in the third (14). Anxiety and cancer worry were the reported outcomes.

All 3 studies assessed anxiety by using the short form Spielberger State-Trait Anxiety Inventory (80). The randomized, controlled trial (13) observed an increase in anxiety scores in the intervention group compared with the control group at 1 and 2 weeks after the intervention. However, group scores did not differ 3 months after the intervention (34.15 in the intervention group vs. 34.76 in the control group). Postintervention anxiety scores decreased in 1 uncontrolled study (15) and did not change in the other (14) compared with baseline.

Table. Summary of Reviewed Studies

<table>
<thead>
<tr>
<th>Question and Comparison or Condition</th>
<th>Study Type</th>
<th>Studies (Reference), n</th>
<th>Risk for Study Bias, n</th>
<th>Participants, n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health behavior effect of family history taking</td>
<td>Family history vs. no intervention</td>
<td>Uncontrolled</td>
<td>2 (11, 12)</td>
<td>– 0 2</td>
</tr>
<tr>
<td></td>
<td>Adverse effects of family history taking</td>
<td>Family history vs. routine care</td>
<td>Randomized, controlled trial</td>
<td>1 (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family history vs. no intervention</td>
<td>Uncontrolled</td>
<td>2 (14, 15)</td>
</tr>
<tr>
<td>Predictive accuracy of family history items</td>
<td>Cancer</td>
<td>Longitudinal</td>
<td>7 (16, 17, 20, 23–26)</td>
<td>2 5 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-sectional</td>
<td>6 (18, 19, 21, 22, 27, 28)</td>
<td>0 4 2</td>
</tr>
<tr>
<td></td>
<td>CHD</td>
<td>Longitudinal</td>
<td>5 (29–33)</td>
<td>1 4 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-sectional</td>
<td>3 (34–36)</td>
<td>0 3 0</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Longitudinal</td>
<td>3 (37–39)</td>
<td>1 2 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-sectional</td>
<td>– – – –</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Longitudinal</td>
<td>5 (40–44)</td>
<td>3 1 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-sectional</td>
<td>12 (45–56)</td>
<td>0 12 0</td>
</tr>
<tr>
<td>Accuracy of family history reporting</td>
<td>Case–control</td>
<td>8 (57, 61–64, 66, 70, 78)</td>
<td>7 0 1</td>
<td>Case patients, 3512; control participants, 4269</td>
</tr>
<tr>
<td></td>
<td>Longitudinal</td>
<td>2 (75, 76)</td>
<td>2 0 0</td>
<td>4648</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
<td>13 (58–60, 65, 67–69, 71–74, 77, 79)</td>
<td>2 1 10</td>
<td>5047</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease.

* Maximum available for analysis.
One uncontrolled study (14) observed no overall change in cancer worry (81). Subgroup analyses indicated that high-risk respondents who were subsequently assessed as low risk at specialist assessment had higher postintervention cancer worry scores than the other respondents.

The randomized, controlled trial provides limited evidence that collecting family history and personalizing risk information is not associated with adverse psychological effects at 3 months. The findings of the uncontrolled studies (14, 15) are consistent with a lack of adverse effects but are undermined by lack of control groups, low participation rates, and possible lack of statistical power. We found considerable heterogeneity in the format of the family history intervention across the 3 studies.

Key Elements of a Family History for Risk Assessment Purposes

We reviewed 20 longitudinal and 21 cross-sectional studies that both reported family history definitions and presented analyzable data for breast cancer (4 studies [16–19]), colorectal cancer (3 studies [20–22]), prostate cancer (6 studies [23–28]), coronary heart disease (8 studies [29–36]), stroke (3 studies [37–39]), and diabetes (17 studies [40–56]) (Appendix Table 5, available at www.annals.org). Forty different definitions of positive family history were used. Few incorporated an age of onset or lineage criteria, and none had an explicit ancestry criterion. The disease frequency in studies ranged from less than 1% to 21%, and the proportion of study participants meeting any given definition of positive family history ranged from 0.3% to 60%. For the longitudinal studies, follow-up ranged from 1 to 20 years.

Sensitivities ranged from 0.01 to 0.51 and specificities from 0.66 to 0.99 across all longitudinal studies and definitions (Appendix Table 6, available at www.annals.org). We observed the highest sensitivities for the definitions “1 or more affected parents” in coronary heart disease, stroke, and diabetes (0.1 to 0.51) and “1 or more affected first-degree relatives” in breast and prostate cancer (0.05 to 0.26). Corresponding specificities were 0.66 to 0.95 and 0.88 to 0.97, respectively. Only “1 or more affected first-degree relatives” was examined for colorectal cancer. Sensitivities ranged from 0.13 to 0.14 and specificity was 0.92.

We observed lower sensitivities for definitions that specified the relative whose status was of interest or required more than 1 relative to be affected.

Sensitivities ranged from 0 to 0.83 and specificities from 0.48 to 1.00 across all cross-sectional studies and definitions. Five studies permitted meaningful within-population comparisons of more than 1 definition (for prostate cancer [27], coronary heart disease [35], and diabetes [41, 50, 53]). Our findings were similar to those for longitudinal studies. The most extensive comparisons were available for diabetes, for which several definitions produced similar sensitivities (“1 or more affected second-degree relatives,” “1 or more affected first-degree relatives or 2 or more affected second-degree relatives,” and “1 or more affected first-degree relatives and 1 or more affected second-degree relatives in same lineage”; “1 or more affected first-degree relatives”; “both parents affected”; and “2 or more affected second-degree relatives from same lineage”). We observed lower sensitivities and higher specificities for definitions that specified the affected relative of interest, required more than 1 relative to be affected, or included an age of onset criterion in the affected relative.

Both the longitudinal and cross-sectional studies showed considerable heterogeneity in underlying disease frequency, proportion of participants who fulfilled criteria for any given definition of positive family history, method of collection, and case definition and ascertainment. Study conclusions are derived from individual studies that compared more than 1 family history definition. For prediction of disease, consistent but weak evidence from the longitudinal studies across different conditions indicates that the highest sensitivities are obtained when definitions focus on disease history in parents or first-degree relatives and that sensitivities decrease with the addition of further required elements. In general, specificities varied inversely with sensitivities. The evidence from the cross-sectional studies is similar for family history as an indicator of prevalent disease, but it is insufficient to draw conclusions because too few comparisons were available.

Accuracy of Family History

Twenty-three studies evaluated the accuracy of reporting family history (Appendix Tables 7 and 8, available at www.annals.org). Informants in these studies had cancer (57–72), diabetes (73–76), hypertension (74–77), cardiovascular disease (75, 76, 78, 79) and were recruited from clinics, disease registries, or population cohort studies (75, 76). In the case–control studies, unaffected participants (57, 61–64, 66, 70, 78) were recruited from the community or identified through administrative databases. Family history was collected in face-to-face interviews (57, 61, 63, 65, 69, 72, 74, 76, 78), mailed surveys (58, 60, 62, 64, 68, 71, 75), or telephone interviews (59, 67, 70, 73). One study (69) did not report the mode of collection. Most reports did not provide detailed information on the type or extent of family history questioning, except for the type of relative of interest. Relatives’ actual disease status was verified by using medical records, disease or death registers, or personal contact. Many studies used more than 1 verification method.

Four studies (61, 63, 66, 70) examined reporting of any type of cancer or any type of heart disease (78) in relatives; 2 longitudinal studies (75, 76) evaluated cohorts with varying prevalence of diseases (hypertension, diabetes, cardiovascular disease, stroke, and asthma). The remaining studies each examined family history of a condition with which the informant was also affected. For reporting of family history of cancer, we observed specificities (correct
reporting of absence of disease in relatives) of 0.91 to 1.00. The sensitivities (correct reporting of presence of disease in relatives) were generally more variable and had wider CIs. The ranges differed by type of cancer (breast, 0.72 to 0.95; colon, 0.33 to 0.90; ovarian, 0.42 to 0.83; and prostate, 0.47 to 0.79). For family history of diabetes, hypertension, and cardiovascular disease, most studies showed sensitivities in the range 0.18 to 0.89, with somewhat higher specificities (0.76 to 0.98). Two studies showed higher sensitivities for reporting family history of hypertension (74) and cardiovascular disease (78).

Six of 8 case-control studies (61, 63, 64, 66, 70, 78) allowed direct comparison of reporting accuracy between affected and unaffected informants. We observed similar specificity for case patients and control participants across all studies but variable sensitivity, with no clear pattern by disease. One longitudinal study (76) showed no effect of participant risk factors on accuracy, whereas a second study (75) showed that probands with disease were less accurate.

We observed no clear association between accuracy and informant age (57, 61–63, 66–68, 70, 76), sex (61–63, 67, 68, 70, 76), or education level (61–63, 67, 68, 70). Four studies (59, 60, 63, 68, 73) showed consistently lower accuracy of reported disease history in second- and third-degree relatives.

Most of the studies that evaluated accuracy of family history reporting related to cancer. They provide fair but consistent evidence that informants are better at correctly reporting absence of disease in relatives (specificity) than history of disease (sensitivity). The samples studied were generally highly selected and were not typical of primary care (spectrum bias). In some studies, investigators used different methods to verify the relatives’ status (verification bias) and did not apply them consistently. In some studies, the verification of relatives’ status may have been done with the knowledge of the reported family history (blinding bias). All of these biases may lead to an overestimation of accuracy.

**DISCUSSION**

We conducted this review to summarize evidence relevant to collecting and using family history in primary care. We found serious methodological limitations with the evidence on effects of collecting family history as a way to promote uptake of preventive interventions—it is insufficient to draw conclusions. The studies of the psychological effects of taking family history do not suggest particular cause for concern but also do not provide definitive evidence that taking a family history is a harmless activity. Only 1 study (13) examined effects of taking family history as part of a typical primary care activity (the periodic health examination).

Taking a family history in primary care needs to be simpler than for the standard comprehensive pedigree taken in clinical genetics (82). Four-generation pedigrees are also unlikely to be helpful in assessing the risk for complex, non-Mendelian disorders (such as those we evaluated) in most patients. Empirically based estimates of the minimum family history information that provides useful predictive power (83) would be more useful, as would confidence that the basic data (reports of relatives’ disease status) are sufficiently accurate for this purpose. Finally, clinical usefulness depends on the improvement of patient outcomes as a result of this exercise. To evaluate family history—based risk assessment as a clinical intervention, controlled trials are needed to ensure that intervention effects are not confounded by psychological and behavioral patterns that participants have formed on the basis of living with “a family disease” (84, 85).

Few of the predictive accuracy studies we reviewed were designed to address our specific question. Almost all were classical epidemiologic investigations that assessed associations between family history and disease. The metrics used to assess strength of etiologic association between family history and disease (such as relative risk) are inappropriate for assessing how well family history classifies risk at an individual level (86). Although many of the studies we reviewed reported evidence of strong associations, as judged by relative risk and similar metrics (full data available at www.ahrq.gov), our analyses indicate that few studies achieved sensitivities much greater than 25%—regardless of the definition used.

The longitudinal analyses provided insight into different definitions of family history and their prediction of a patient’s future disease risk. In contrast, the cross-sectional analyses provided information on the effectiveness of family history for identifying current disease. Given the generally low sensitivities, simple definitions based on first-degree relatives—or parental history without further elaboration—performed best. Some of the longitudinal studies were of high quality, but their heterogeneity constrained quantitative integrative analysis. The cross-sectional studies varied more in quality. Because many studies included persons who knew they had the condition of interest, we could not determine whether receiving the diagnosis had influenced the accuracy of their family history reporting or whether knowledge of their family history had led to an earlier diagnosis.

Capturing family history often involved questionnaires or interviews designed for epidemiologic research, which are not necessarily typical of current primary care practice. However, many of the definitions were simple and probably give an indication of the types of answers that would be received if elicited verbally as part of an office consultation. Although simple definitions of positive family history might not carry a high sensitivity for predicting or detecting complex disorders, they might still improve the predictive ability of other established risk factors. This might make a difference in which preventive interventions physicians recommend or how they triage patients for risky or costly screening tests (86, 87). Also, routine family
history assessment may help to identify the small proportion of persons seen in primary care whose distinct familial disease pattern might indicate an underlying genetic predisposition that merits more extensive assessment by a geneticist.

For family history to be of value in clinical decision making, patients must report—and primary care practitioners must be able to ascertain—accurate family history information. An accurate family history is both sensitive (correctly identifying disease in relatives) and specific (correctly identifying lack of disease in relatives). When we explored questions about accuracy, we reviewed studies that were conducted in specialized clinical settings; the applicability of the findings from these studies to primary care settings may be limited. Our analyses were constrained by lack of reporting of characteristics of interest, particularly in relation to relatives. Overall, fair-quality evidence suggests that informants are better at identifying absence of disease in relatives (specificity) than at correctly reporting relatives who have been affected (sensitivity). The accuracy of family history reporting cannot be separated from the performance of the methods used to gather family history. We observed great variation in how family history was captured but could not perform a formal analysis.

Our review was largely limited to populations and settings applicable to primary care. Systematic family history collection and interpretation in specialist settings may provide evidence relevant to primary care; however, scope and pragmatic considerations limited our focus. Our emphasis on specific clinical behavioral outcomes also did not allow us to explore other effects on the part of patients, such as seeking out more extensive information from family members as a result of having been asked “the first” set of questions on family history.

Well-designed trials are required to compare the effect of clearly described, family history–based, personalized risk advice interventions with that of standard care on clinically relevant outcomes, including risk-reducing behaviors, mortality, morbidity, and evidence-based surrogate measures. Investigators also need to examine psychological effects and family and social sequelae, by using appropriate and validated instruments, and explore the effects on persons who decline to participate. Any further studies of the predictive ability of family history elements should take the way in which family history information is actually used in routine practice into account; for example, whether it is used in isolation or in combination with other risk factor data. It is debatable whether priority should be given to further studies that examine the accuracy of family history reporting in general or to those that evaluate the specific attributes of family history tools that promote accurate reporting. If further accuracy studies are conducted, attention should be given to the populations of interest and spectrum of disease risk represented.

Many health professionals regard family history en-quiry as a standard element of good medical care. Occa-

sionally, family history questions reveal unusual familial disease patterns and prompt specialist investigation. Primary care practitioners can also gain insight into patients’ experiences of disease within the family, which are relevant to framing preventive advice. However, many questions remain regarding whether information gained from family history assessment improves risk prediction and chronic disease risk management, the best way to collect such information, and the positive and negative effects such collection has on patient outcomes.

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