Published in final edited form as:

Genet Med. 2011 November ; 13(11): 956–965. doi:10.1097/GIM.0b013e3182241d88.

Clinical utility of family history for cancer screening and referral in primary care: A report from the Family Healthware Impact Trial

Wendy S. Rubinstein, MD, PhD^{1,2}, Louise S. Acheson, MD, MS^{3,4,5}, Suzanne M. O'Neill, MS, PhD^{1,6}, Mack T. Ruffin IV, MD, MPH⁷, Catharine Wang, PhD, MSc⁸, Jennifer L. Beaumont, MS⁹, and Nan Rothrock, PhD⁹ for the Family Healthware Impact Trial (FHITr) Group

¹Department of Medicine, Division of Genetics, NorthShore University HealthSystem (previously named Evanston Northwestern Healthcare), Evanston, Illinois

²Department of Medicine, University of Chicago Pritzker School of Medicine, Chicago, Illinois

³Department of Family Medicine, Research Division, Case Western Reserve University

⁴University Hospitals Case Medical Center

⁵Case Comprehensive Cancer Center, Cleveland, Ohio

⁶Department of Medicine, Northwestern University, Chicago, Illinois

⁷Department of Family Medicine, University of Michigan, Ann Arbor, Michigan

⁸Department of Social and Behavioral Sciences, Boston University School of Public Health, Boston, Massachusetts

⁹Department of Medical and Social Sciences, Northwestern University, Chicago, Illinois

Abstract

Purpose—To assess the effectiveness of computerized familial risk assessment and tailored messages for identifying individuals for targeted cancer prevention strategies and motivating behavior change.

Methods—We conducted a randomized clinical trial in primary care patients aged 35–65 years using Family Healthware, a self-administered, internet-based tool that collects family history for six common diseases including breast cancer, colon cancer, and ovarian cancer, stratifies risk into three tiers, and provides tailored prevention messages. Cancer screening adherence and consultation were measured at baseline and 6-month follow-up.

Results—Of 3283 participants, 34% were at strong or moderate risk of at least one of the cancers. Family Healthware identified additional participants for whom earlier screening (colon cancer, 4.4%; breast cancer, women ages: 35–39 years, 9%) or genetic assessment (colon cancer, 2.5%; breast cancer, 10%; and ovarian cancer, 4%) may be indicated. Fewer than half were

Copyright © American college of Medical Genetics.

Wendy S. Rubinstein, MD, PhD, Center for Medical Genetics, NorthShore University HealthSystem, 1000 Central St., Suite 620, Evanston, IL 60201. wrubinstein@northshore.org.

Disclosure: The authors declare no conflict of interest. Submitted for publication February 2, 2011.

These findings were presented, in part, at the American Society for Preventive Oncology Annual Meeting, Rockville, MD, March 22, 2010, the National Institutes of Health State-of-the-Science Conference on Family History and Improving Health, Bethesda, MD, August 24, 2009, and the FHITr Working Group Preliminary Results Meeting, at the Centers for Disease Control and Prevention, Atlanta, GA, December 16, 2008.

already adherent with risk-based screening. Screening adherence improved for all risk categories with no difference between intervention and control groups. Consultation with specialists did not differ between groups.

Conclusion—Family Healthware identified patients for intensified cancer prevention. Engagement of clinicians and patients, integration with clinical decision support, and inclusion of nonfamilial risk factors may be necessary to achieve the full potential of computerized risk assessment.

Keywords

family history; risk assessment; early detection of cancer; neoplasms; health knowledge; attitudes; practice

Family history is a well-established risk factor for breast cancer,^{1,2} colorectal cancer,^{3,4} and ovarian cancer.⁵ Family history-based risk assessment for cancer and other common diseases has potential utility to guide or to motivate risk-specific strategies to reduce the disease burden for individuals, families, and populations. Prevention and early detection protocols for these cancers vary according to familial risk.^{6–17} Genetic counseling is recommended for people at increased risk for hereditary cancer susceptibility, and earlier screening for breast and colon cancer is indicated for a moderate or strong family history.^{18,19}

In 2009, the National Institutes of Health convened a State-of-the-Science Conference to review the scientific foundation for using family history information about common diseases in primary care.²⁰ The evidence-based review²¹ found a dearth of controlled interventional trials evaluating the clinical utility of family history assessment; two studies demonstrated improvement in primary care/general population settings for mammography screening, breast self-examination, and clinical breast examination with systematic collection of family history.^{22,23}

Recognizing that family health history is rarely used to its full potential in practice, the Centers for Disease Control and Prevention (CDC) developed Family Healthware, an interactive, internet-based tool that guides users to record family history, stratifies familial risk for coronary heart disease, stroke, diabetes, and colon, breast, and ovarian cancers, and provides risk-based recommendations for screening tests and lifestyle changes.²⁴ The CDC selected three academic centers that designed and conducted the Family Healthware Impact Trial (FHITr) to evaluate the clinical utility of Family Healthware. Because most preventive services are delivered in primary care,²⁵ the effects of Family Healthware on preventive care were evaluated by a randomized trial in primary care practices. We have previously reported that using Family Healthware increased patients' fruit and vegetable intake and physical activity but appeared to decrease cholesterol screening and did not affect smoking nor screening for diabetes.²⁶

We hypothesized (1) that Family Healthware would identify participants eligible for additional cancer screening and referrals because of their family history-based risk of cancer and (2) that patients who recorded their family history and received specific cancer prevention messages tailored to their familial risk levels would be more likely to adhere to risk-appropriate cancer screening than patients who did not have their family history assessed and who received generic (not personalized) prevention messages. In this study, we report the number of additional candidates identified for cancer screening because of familial risk and the effect of using Family Healthware on cancer screening and consultation with specialists (including genetics consultation) related to breast, ovarian, and colon cancers.

MATERIALS AND METHODS

Complete details of Family Healthware design²⁴ and FHITr study design and surveys²⁷ have been published elsewhere and are briefly summarized in this study. Family Healthware is an interactive, self-administered, internet-based tool that collects data on disease history of first- and second-degree relatives and health behaviors and screening tests. A set of software algorithms in Family Healthware analyzes and stratifies familial risk into three tiers (strong, moderate, weak) based on the number of relatives affected, their age at disease onset, their sex, the degrees of relationship, and certain combinations of cancer in the family within the same lineage.²⁸ For example, the algorithm for familial colon cancer risk considers family history of both colon cancer and ovarian cancer; breast cancer risk assessment takes into account breast cancer and ovarian cancer; and ovarian cancer risk assessment factors in family history of colon, breast, and ovarian cancers. Clinical validity (accuracy of disease risk prediction) of the Family Healthware cancer risk algorithms seems to be fair, as gauged by comparison to population-based risk stratification in unaffected individuals.²⁹ A second set of algorithms generates tailored prevention messages based on familial risk level, sex, age, reported health behaviors (physical activity, diet, smoking, alcohol use, and aspirin use), and screening history.²⁴

FHITr used a practice-based cluster-randomized design whereby 41 primary care practices (internal medicine, family medicine, and obstetrics-gynecology) were randomized into intervention or control arms. Participants were healthy adults aged 35–65 years. Exclusion criteria included a personal history of coronary heart disease, diabetes, stroke, or any cancer other than nonmelanoma skin cancer, the inability to speak or read English, and known pregnancy. Potential participants were systematically identified from the practices' patient schedules and records. Patients received invitation letters signed by their primary care physicians. Physicians' study participation entailed signing the invitation letters and permitting access to schedules and charts. All participants were asked to share the printed prevention messages with their physicians. Active modes of delivery of study messages varied among study sites: printed messages were provided in person to the participant at a scheduled primary care visit (two sites) and provided to the physician either with the patient's permission or without or sent to the participant by e-mail or mail (one site). A resource manual was provided to all physician practices summarizing screening recommendations and prevention strategies (analogous to those used for the programming of tailored messages in Family Healthware), with citations. Study protocols were approved in 2004 by institutional review boards at all three centers, and a combined protocol was approved by the CDC's institutional review board. Informed consent was obtained from all subjects. Recruitment took place from November 2005 to March 2007.

Intervention and control groups each completed an identical online 128-question baseline survey assessing health behaviors, lifestyle choices, risk perceptions, and communication about family health history. The intervention group completed Family Healthware following the baseline survey and received personalized risk assessment and tailored prevention messages generated by Family Healthware. Intervention messages consisted of the following: Weak familial risk—reinforce standard prevention recommendations; Moderate risk—personalized prevention recommendations; and Strong risk—personalized prevention recommendations and referral to specialist. Control subjects received generalized (not personalized) prevention messages following completion of the baseline survey. Each group completed an identical follow-up survey at 6 months. The control group then completed Family Healthware, to allow for familial risk stratification. Table 1 gives examples of intervention and control breast cancer risk and prevention messages received on-screen and in printable form. Surveys and Family Healthware could be completed online at the study website (all three study sites), at a computer in the physician's office (one site), or by a

structured telephone interview (two sites) to facilitate enrollment of noncomputer literate individuals. Colorectal cancer was referred to as “colon cancer” in materials read by participants (e.g., Family Healthware tool and messages); for consistency, we preferentially use the term “colon cancer” in this article, although recognizing that in general “colorectal” is the proper usage.

Only participants who completed the baseline assessment, 6-month follow-up assessment, and Family Healthware (in proper sequence) are included in analyzing the effects of the intervention. For women aged 35–40 years, adherence to clinical breast examinations could not be accurately assessed because the longest response category was “3 or more years ago”; therefore, these participants were excluded from these analyses. Analyses of screening excluded those with an interim diagnosis of cancer, as it was not possible to determine whether tests or consultations were performed for screening or diagnostic purposes. However, as cancer diagnosis is a potential outcome of the study intervention, we report the characteristics of the individuals in control and intervention groups who were diagnosed with cancer during the follow-up period.

Analysis

Measures of cancer screening behaviors—Measures of cancer screening behavior included self-reported completion of screening tests for each cancer and uptake of referral to a specialist. Self-reported cancer screening adherence was determined for each participant in two ways: (1) adherence to screening that is recommended for the general population at average risk and (2) adherence to “risk-based” screening for which participants were eligible according to familial risk level, as assessed by Family Healthware. Participants at “Weak” familial risk were eligible for cancer screening as recommended for the general population. Screening adherence definitions for breast and colon cancer are provided in Table 2. The recommendations based on familial risk were those in effect at the time when the FHITr study was conducted.^{6–17} Risk level definitions were based on published data and expert recommendations: breast cancer—weak,⁶ moderate,^{7–10} and strong^{7–13} and colon cancer—weak,¹⁴ moderate,^{15–17} and strong.^{15,17} Women aged 35–39 years at strong risk were counted as adherent if they had ever had a mammogram.

Because colon cancer screening recommendations could be satisfied by having fecal occult blood testing, sigmoidoscopy, or colonoscopy within the recommended time interval, we developed a composite colon cancer screening definition where “adherent” means that the patient has satisfied screening recommendations for one or more modality.

In contrast to breast cancer and colon cancer, ovarian cancer does not have any evidence-based, strongly supported screening recommendations, and screening is advised against for average-risk women.³⁰ Women at moderate or strong risk were recommended to talk with their health professional about their family history, how it affects their risk, and options for prevention and screening (such as blood CA-125 and ultrasound).^{31–33} Although there is no standard for screening adherence, we examined the impact of the intervention on women with ovaries having CA-125 and/or transvaginal ultrasound during the follow-up.

Analysis of participants eligible for additional cancer screening and referrals

—Adherence at baseline to “general population” and “risk-based” screening recommendations for colon cancer and breast cancer was compared between intervention and control groups and among familial risk categories. Comparisons between intervention and control groups used generalized estimating equation-based logistic regression models to account for cluster randomization. No significant differences were found between the experimental groups; therefore, to improve power, we combined intervention and control groups to describe participants eligible for heightened cancer screening and referrals.

Analysis of outcomes: Cancer screening and referrals—Subjects who were adherent to risk-appropriate screening at baseline were excluded from screening change analyses. Subjects with “room to improve” at baseline included individuals who were eligible for a screening test based on age, sex, and familial risk level but were not adherent with screening. Odds ratios and *P* values were obtained from a generalized estimating equation-based logistic regression model to account for cluster randomization. Odds ratios are reported for improvement in intervention versus control groups. Analyses were performed within each risk group (e.g., strong, moderate, and weak), comparing intervention with control. Analyses were also performed for all intervention versus all control subjects, adjusted for risk and baseline screening status. Messages about referral for consultation were restricted to the strong risk intervention group; therefore, we combined the weak and moderate risk groups for analyses of referral behaviors.

Subjects were asked the following questions about consultations: “In the last six months, have you visited a medical professional (such as a genetic counselor, etc.) other than your regular doctor because of concerns about cancer?” and “In the last six months, have you consulted a genetic specialist, had genetic counseling or genetic testing, other than for fertility, prenatal care or childbearing?” For analysis of consultations, subjects were sorted into weak/moderate and strong “cancer risk groups,” where strong cancer risk was defined as having at least one strong risk for breast, ovarian, or colon cancer. Generalized estimating equation-based logistic regression models were used to compare intervention and control arms, within each cancer risk group.

Posthoc power calculations were based on two-group comparison of independent proportions at 5% level of significance.

RESULTS

Demographic characteristics of the study sample

Of the 4248 patients who volunteered for the study, 3786 completed the baseline survey. Overall, the study had an 18% recruitment rate, an 89% retention rate from time of consent to completion of the baseline survey, and an 88% retention rate from baseline to follow-up. The distribution of participants by primary care specialty was Family Practice 1834 (48%), Internal Medicine 1485 (39%), and Obstetrics/Gynecology 467 (12%). The study population had a mean age of 50.6 years and was mostly white (91%), female (70%), married (76%), insured (97%), highly educated (72% college graduates), and high income. The distribution of demographic characteristics across the two study arms is summarized in Table 3. Although statistically significant differences exist with respect to many of the characteristics when analyzed without any adjustments, no statistically significant demographic differences between control and intervention groups remained when we controlled for the practice level clustering. After the exclusions described above (e.g., individuals with an interim diagnosis of cancer), 3283 participants were available for analysis regarding the effects of the intervention.

Distribution of familial cancer risks

Table 4 shows that there were no differences between study arms in the distribution of participants among family history risk categories for the three cancers. Thirty-four percent of study participants were found to be at strong or moderate risk for at least one of the three cancers.

Baseline cancer screening

Based on recommendations for the general population (not on familial risk), study participants who were eligible for screening had very high rates of adherence for breast and colon cancer, as summarized in Table 5. For example, overall baseline adherence to screening recommended for the general population was 79% for colon cancer, 76% for mammograms, and 96% for clinical breast examinations. Screening adherence rates did not differ at baseline between the study arms. For colon cancer screening, study participants were adherent with screening by fecal occult blood testing (359/1871 = 19%), flexible sigmoidoscopy (284/1871 = 15%), and colonoscopy (1336/1871 = 71%). There was no difference between the study arms on these screening methods ($P > 0.17$). Study participants at moderate and strong risk for breast or colon cancer were more likely to be current if eligible for breast or colon cancer screening according to general population guidelines, compared with those who were not at increased familial risk ($P = 0.01$).

At baseline, among female participants with intact ovaries, only 114 (5%) had ever had a serum CA-125 and 678 (32%) had ever had a transvaginal ultrasound. The rates were not significantly different between the two study arms ($P > 0.32$).

Identification of participants eligible for additional cancer screening and consultation

Family Healthware identified 145 participants (4.4% of 3283 total intervention and control participants) who may be candidates for earlier and more frequent colon cancer screening because of increased familial colon cancer risk (Table 5). Thirty-five were at strong and 110 at moderate familial risk of colon cancer. Only 43% of these participants had obtained the indicated screening before study enrollment. Family Healthware identified 24 women (9% of 267 participants aged 35–39 years) at strong risk of breast cancer, eligible for breast cancer screening earlier than 40 years of age. Of these, only four (17%) had received a mammogram before study enrollment.

Individuals at strong familial cancer risk were eligible for genetic risk assessment. Two and a half percent (83/3283) of participants were at strong risk of colon cancer, 9.8% (321/3283) at strong risk of breast cancer, and 3.9% (128/3283) at strong risk of ovarian cancer (Table 4). Only 3% of participants had undergone genetic consultation or genetic testing before study enrollment for concerns about cancer.

Effect of Family Healthware intervention on cancer screening among participants not adherent at baseline

As summarized in Table 6, there was no significant difference between groups in the percent of study participants moving from not adherent to adherent with colon cancer screening in any familial risk category. Because of high baseline screening rates, the power to detect a difference between the study arms was 0.06.

There was no significant difference between the study arms in the percent of women becoming adherent with mammography by familial risk category (Table 6). Because of high baseline adherence, the power to detect a difference between the study arms was 0.19. Almost all women were adherent to clinical breast examinations at baseline. There was no significant difference between the study arms in the percent of women becoming adherent with clinical breast examination by familial risk category (data not shown).

During the follow-up of 6 months, 47 (2%) women with ovaries got a CA-125 and 100 (5%) had a transvaginal ultrasound. There was no measurable difference between the study arms ($P > 0.09$).

Analyses including all participants (including those up-to-date on screening at baseline) showed that both intervention and control groups equally increased their adherence to risk-based colon cancer screening and mammography. The intervention group went from 76% adherent to risk-appropriate colon cancer screening at baseline to 84% adherent at follow-up, whereas the control group improved from 77% adherent to 84% at follow-up ($P = 0.95$ for comparison between study arms, adjusting for practice clustering, risk, and baseline adherence). Similarly, risk-based mammogram screening adherence increased from 73 to 82% in the intervention group and from 78 to 85% in the control group ($P = 0.82$ for comparison between study arms). There was no significant difference in cancer screening at follow-up among participants who received messages that their family history was a “Weak” risk factor for cancer, compared with those in the control group (data not shown).

Consultations about cancer risk

Only 11 (six intervention and five control) subjects reported that they had visited a genetic specialist during the 6-month follow-up period. Differences between intervention and control groups in self-reported consultation with a medical specialist about cancer risk at follow-up were examined for 2895 subjects at weak or moderate risk for all three cancers and 383 subjects at strong risk for at least one cancer. No statistically significant differences were found for the weak/moderate risk subjects (2.4% intervention vs. 3.1% control, $P = 0.27$) or the strong risk subjects (6.2% vs. 7.0%, $P = 0.79$) for consultation with a specialist about cancer risk.

Characteristics of participants diagnosed with cancer

Because the questionnaire did not distinguish screening from diagnostic procedures and consultations, the 34 participants who reported a cancer diagnosis between the baseline and follow-up assessments were excluded from analyses of screening adherence. However, as cancer diagnosis is a potential study outcome, the characteristics of these individuals are reported in this study. Seven participants reported a new breast cancer diagnosis (five in the intervention group and two in the control group); 27 reported “other” cancer; and none reported a colon cancer or ovarian cancer diagnosis. The characteristics of patients reporting breast cancer were five of seven adherent with mammograms, all seven adherent with clinical breast examination at baseline. Breast cancer risk levels were moderate = 3 and weak = 4. Only two of these women were not up to date on their mammogram screening and had “room to improve.” The distribution of the patients reporting “other” cancer were intervention $n = 17$ and control $n = 10$.

DISCUSSION

Family Healthware, a self-administered, internet-based tool, was used by primary care adult patients to record their family history outside of the clinician-patient encounter and to receive tailored familial disease risk and prevention information. Elevated familial cancer risk was highly prevalent: 34% of participants were at strong or moderate risk for at least one of the three cancers. Before enrollment, participants at increased familial risk for colon or breast cancer were more likely than those with low familial risk to be adherent if eligible for cancer screening recommended for the general population of their age and sex. Family Healthware also identified that 4.4% of all participants were potentially eligible for colon cancer screening beyond that recommended for the general population, and 9% of female participants aged 35–39 years seemed eligible for earlier breast cancer screening. Furthermore, a sizeable percentage of all participants—approximately 2.5% for colon cancer, 10% for breast cancer, and 4% for ovarian cancer—were potential candidates for genetic risk assessment. However, fewer than half of the additional participants, for whom colon cancer screening was indicated based on family history, were adherent with risk-based

colon cancer screening, and a mere 17% of eligible women aged 35–39 years had obtained early mammography. Consultation for familial cancer risk was rare, reported in only 3% of participants at baseline. Therefore, Family Healthware identified a group at increased cancer risk in need of targeted preventive measures.

Although small in absolute numbers, those at strong risk represent a group in whom screening and referral are of the utmost importance. Referral of these individuals for genetic counseling and cascade genetic testing within their families is a powerful way to focus screening recommendations for many of the highest risk individuals within a population.^{34,35}

We hypothesized that tailoring preventive recommendations on an individual's family history of breast, ovarian, and colon cancers should increase the percentage of patients completing these recommendations, especially from a population of adults aged 35–65 years with an established primary care provider relationship. In this setting, both the Family Healthware intervention and the standard prevention messages were associated with an increase in the percentage of adults adherent with screening for breast or colon cancer 6 months later. However, there was no significant difference in screening rates between the control group and the group using Family Healthware, either as a whole or within levels of familial risk. Thus, we also found no evidence that tailored messages conveying information about weak familial risk resulted in complacency about cancer screening. Conversely, there was no evidence that use of Family Healthware resulted in overscreening for those at weak risk.

The FHITr demonstrated the feasibility of implementing self-administered family history risk assessment in primary care, but conducting this study with unselected, healthy patients limited the enrollment of people in need of screening and the power to detect an effect. The population recruited to the FHITr study had far higher screening adherence rates than a national sample, as measured by the Behavioral Risk Factor Surveillance System.³⁶ FHITr compared with national mammography rates for women aged 40 years or older were 76% vs. 61%, and FHITr compared with national combined fecal occult blood testing/endoscopic colon cancer screening rates for adults age 50 years or older were 79% vs. 60%.³⁶ This reflects the sociodemographic features of our study population such as having private insurance, being non-Hispanic white, a higher education level, and having a physician,^{36–38} factors associated with higher cancer screening rates. Furthermore, as others have also observed,³⁸ participants with increased familial risk of a specific type of cancer were more likely to be already up-to-date on screening for that type of cancer, before study enrollment. The resulting ceiling effect left only a small proportion of participants in whom effects of the intervention could be observed. Smaller still was the proportion of subjects who had strong or moderate familial cancer risks. The posthoc power to detect a difference between the overall intervention versus control group ranged from 0.19 for mammogram screening to 0.06 for colon cancer screening.

The nature of the study as an evaluation of a computerized health tool may have created a perceived need for computer literacy and access and thereby limited the diversity of the study population. We attempted to mitigate this effect by facilitating participation for those without internet access at home. Participants could complete the study by phone by interview or in the clinic. Telephone assistance was used in lieu of direct computer access by 9% of the study subjects, and there were no significant demographic differences among groups using these two modes of study participation.²⁷

The greatest potential to measure the effect of an intervention (and to serve that group) is in a population where baseline adherence is low. Paradoxically, however, barriers to healthcare

will be larger in a group with lower levels of insurance, household income, and education. Recruitment may also be more challenging. Therefore, we believe that in designing future studies of this kind, strategies will be needed to reach eligible subjects who have not been screened. In addition to the medically underserved, it will be important to include younger participants (aged 20 – 40 years) with a strong family history of cancer, as this study demonstrated that the majority of these had not had cancer screening that may have been indicated based on their familial cancer risk.

In addition to the screening behaviors, we measured self-reported visits to a medical professional other than the participant's regular doctor because of concerns about cancer and visits to a genetic specialist or genetic counselor. Either event was extremely rare and was not influenced by the Family Healthware messages. We are not able to determine whether physicians made the recommendation to see such a provider.

Although it may seem surprising that the study participants at strong risk did not avail themselves of cancer genetics services, low rates of genetic assessment have been a recurrent theme, even in academic settings. For example, evidence of physician referral was found for only 7% of high-risk patients who were seen at a National Cancer Institute-funded comprehensive cancer center ambulatory clinic and used a patient-administered computerized cancer risk assessment program.³⁹ A study of computerized risk assessment among patients with breast cancer in an academic medical oncology setting suggested that referral uptake was reflected by stages of readiness that were not traversed for all patients within a 6-month period,⁴⁰ the time frame of our study. Recognizing that opportunities for colonoscopy or mammography screening might be limited during the 6-month follow-up period, FHITr used a modified Stages of Change model as an intermediate outcome measurement of intention to screen.^{41,42} Intention to undergo any cancer screening, as assessed by the Stages of Change measures, did not differ significantly between study arms (data not shown).

The full set of Family Healthware tailored messages for all six diseases ranged from 8 to 15 pages depending on the familial risks. Clearly, there is a chance that the messages were not fully read by the study participants. Furthermore, the added exhortation to action in the tailored prevention recommendation when compared with the standard messages (Table 1) may have been too subtle and may not have been fully appreciated by the participants. One interpretation of our results is that a written message is generally not sufficient as a stand-alone intervention for prompting cancer-related health behavior changes, even when provided in the context of a primary care visit as was the case for most subjects. However, our study may lack sufficient power to state this definitively.

The messages delivered by Family Healthware need to be refined. Because too much information might dilute the message and paradoxically lead to inaction, the importance of various elements of the message in prompting behavior change should be better understood and used as parsimoniously as possible. Family Healthware is programmed to inform individuals about which family history features (affected relatives and early age of cancer diagnosis) led to their strong or moderate risk categorization, because there is some evidence that tailored risk communication based on age, family history, or risk category influences risk perception and screening uptake.^{43,44} However, it is unclear which specific elements of the messages are key. Coupling optimized Family Healthware messages with additional interventions warrants further investigation.

Although screening did not differentially improve in the intervention versus control group, the percentage of all eligible subjects adherent to risk-based screening increased at 6-month follow-up by 7% for colon cancer screening (change from 77 to 84% adherent) and 8% for

mammography (75% to 83% adherent). Among those not up-to-date at baseline, we observed a 60% increase in the proportion current on mammography and a 36% increase in the proportion current on colon cancer screening (Table 6). The increases observed in FHITr are commensurate with effects observed for other practice-based interventions. For example, in a systematic review of strategies for improving colorectal cancer screening,³⁸ the percentage point increase owing to various types of interventions ranged from patient reminders (0–15%; highest figure with a nonsignificant *P* value), education videos or brochures (not effective), decision aids (mixed results; highest 14–23%), and group education (not effective). One-on-one interventions and those focused on eliminating barriers such as access to care and language were associated with a 15–42% increase in screening rates. System-level interventions (e.g., clinician reminders and patient navigators) showed a 7–28% improvement in screening.

Thus, it seems likely that in FHITr both the control activities (baseline questionnaire and generic prevention messages) and the intervention (baseline questionnaire, Family Healthware questionnaire, and family history-tailored prevention messages) served as prompts for patients and clinicians to accomplish cancer screening. All evaluable FHITr subjects completed a baseline survey assessing health behaviors, lifestyle choices, risk perceptions, and communication of family health history. The lengthy survey may have had unintended consequences of leading participants in both groups to ponder over their own health and/or may have been inferred as health recommendations. Two thirds of participants had an upcoming visit with the primary care clinician, offering an opportunity for advising screening, which may have been enhanced by either generic or family history-based prompts. With this study design, effects attributable to Family Healthware itself may have been masked.

In the setting of significant family history for some diseases, there is a risk that healthcare providers may order or patients may request screening tests with no evidence to support a benefit. Indeed, some of the physicians who were asked to participate in the study voiced objections to the use of messages about ovarian cancer screening and even the recommendation that patients speak to their doctor about the issue. Although such conversations may have occurred, our study shows that a low proportion of women in this situation report getting serum CA-125 testing or transvaginal ultrasounds.

The FHITr study provides limited insight into the use that clinicians made, or might make, of the automatically generated family history report and prevention prompts. Noninclusion by Family Healthware of known risk factors such as colorectal polyps, breast biopsy, and gestational diabetes may have limited its utility for clinicians. Despite its computerized format, Family Healthware was not integrated with the electronic medical record during this study; in the future, family history assessment has the opportunity to link risk stratification with clinical decision support.⁴⁵ Factors associated with improved clinical outcomes using clinical decision support systems include automatic provision of recommendations (not only assessments) as part of clinician workflow and using computer-based methods at the time and location of decision making.⁴⁶ Design of future studies and clinical implementation should incorporate these factors to enhance utility of familial risk stratification.

In summary, the FHITr study did not find an effect of family history-based prevention messages on cancer screening or consultation behaviors in a largely white, well-educated, and affluent population whose screening rates were already high at baseline. Unexpectedly high baseline screening rates resulted in low power to detect an intervention effect. Nonetheless, Family Healthware identified a substantial proportion of unscreened participants for whom cancer screening and consultation for risk assessment were recommended based on family history but would not have been recommended for the

general population at average risk. It will be challenging but particularly important to couple risk assessment to a more active intervention than written messages and ultimately to achieve behavior change in a less adherent population. Engagement of clinicians, incorporation of nonfamilial risk factors for comprehensive assessment, and implementation of clinical decision support systems seem to be some of the key factors necessary to achieve the full potential of familial risk assessment.

Acknowledgments

The Family Healthware Impact Trial (FHITr) was supported through cooperative agreements between the Centers for Disease Control and Prevention and the Association for Prevention Teaching and Research (ENH-#U50/CCU300860 TS-1216) and the American Association of Medical Colleges (UM#U36/CCU319276 MM-0789 and CWR# U36/CCU319276 MM0630). Drs. Acheson (K07 CA086958) and Wang (K07 CA131103) also received salary support from the National Cancer Institute.

References

1. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 1989; 81:1879–1886. [PubMed: 2593165]
2. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet.* 1991; 48:232–242. [PubMed: 1990835]
3. Potter JD. Colorectal cancer: molecules and populations. *J Natl Cancer Inst.* 1999; 91:916–932. [PubMed: 10359544]
4. St John DJ, McDermott FT, Hopper JL, Debney EA, Johnson WR, Hughes ES. Cancer risk in relatives of patients with common colorectal cancer. *Ann Intern Med.* 1993; 118:785–790. [PubMed: 8470852]
5. Stratton JF, Pharoah P, Smith SK, Easton D, Ponder BA. A systematic review and meta-analysis of family history and risk of ovarian cancer. *Br J Obstet Gynaecol.* 1998; 105:493–499. [PubMed: 9637117]
6. U.S. Preventive Services Task Force (USPSTF). [Accessed March 29, 2010.] Screening for breast cancer. [online] [cited 2005 September 8], 2002. Available at: <http://www.ahrq.gov/clinic/uspstf/uspstfbrca.htm>
7. American Cancer Society. [Accessed March 29, 2010.] Cancer facts and figures. [online] [cited August 17, 2005], 2005. Available at: <http://www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf>
8. National Comprehensive Cancer Network Clinical Guidelines in Oncology. [Accessed March 29, 2010.] Breast cancer screening and diagnosis. [online] [cited September 10, 2004], 2004. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast-screening.pdf
9. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. *JAMA.* 1997; 277:997–1003. [PubMed: 9091675]
10. National Cancer Institute. [Accessed March 29, 2010.] Genetics of breast and ovarian cancer. [Health professional version, online] [cited November 1, 2004], 2004. Available at: <http://www.nci.nih.gov/cancertopics/pdq/genetics/breast-and-ovarian/healthprofessional/allpages>
11. National Comprehensive Cancer Network Clinical Guidelines in Oncology. [Accessed March 29, 2010.] Genetics/familial high risk assessment. [online] [cited September 10, 2004], 2004. Available at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf
12. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA.* 2004; 292:1317–1325. [PubMed: 15367553]
13. Komenaka IK, Dittkoff BA, Joseph KA, et al. The development of interval breast malignancies in patients with BRCA mutations. *Cancer.* 2004; 100:2079–2083. [PubMed: 15139048]
14. CDC Cancer Prevention and Control. [Accessed March 29, 2010.] Basic facts on screening. [online] [cited August 31, 2005], 2005. Available at: http://www.cdc.gov/cancer/screenforlife/fs_basic.htm

15. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. *Gastroenterology*. 2003; 124:544–560. [PubMed: 12557158]
16. Walsh JM, Terdiman JP. Colorectal cancer screening: clinical applications. *JAMA*. 2003; 289:1297–1302. [PubMed: 12633192]
17. Rex DK, Johnson DA, Lieberman DA, Burt RW, Sonnenberg A. Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. *American College of Gastroenterology. Am J Gastroenterol*. 2000; 95:868– 877. [PubMed: 10763931]
18. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol*. 2010; 28:893–901. [PubMed: 20065170]
19. U S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. *Ann Intern Med*. 2005; 143:355–361. [PubMed: 16144894]
20. Berg AO, Baird MA, Botkin JR, et al. National Institutes of Health State-of-the-Science Conference Statement: family history and improving health. *Ann Intern Med*. 2009; 151:872– 877. [PubMed: 19884615]
21. Qureshi N, Wilson B, Santaguida P, et al. Family history and improving health. *Evid Rep Technol Assess (Full Rep)*. 2009;1–135.
22. Kadison P, Pelletier EM, Mounib EL, Oppedisano P, Poteat HT. Improved screening for breast cancer associated with a telephone-based risk assessment. *Prev Med*. 1998; 27:493–501. [PubMed: 9612841]
23. Giles JT, Kennedy DT, Dunn EC, Wallace WL, Meadows SL, Cafiero AC. Results of a community pharmacy-based breast cancer risk-assessment and education program. *Pharmacotherapy*. 2001; 21:243–53. [PubMed: 11213861]
24. Yoon PW, Scheuner MT, Jorgensen C, Khoury MJ. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. *Prev Chronic Dis*. 2009; 6:A33. [PubMed: 19080039]
25. DeVoe JE, Fryer GE, Phillips R, Green L. Receipt of preventive care among adults: insurance status and usual source of care. *Am J Public Health*. 2003; 93:786–791. [PubMed: 12721145]
26. Ruffin MT, Nease D, Sen A, et al. Effect of preventive messages tailored to family history on health behaviors: the Family Healthware Impact Trial. *Ann Fam Med*. 2011; 9:3–11. [PubMed: 21242555]
27. O'Neill SM, Rubinstein WS, Wang C, et al. Familial risk for common diseases in primary care: the Family Healthware Impact Trial. *Am J Prev Med*. 2009; 36:506–514. [PubMed: 19460658]
28. Scheuner MT, Wang SJ, Raffel LJ, Larabell SK, Rotter JI. Family history: a comprehensive genetic risk assessment method for the chronic conditions of adulthood. *Am J Med Genet*. 1997; 71:315–324. [PubMed: 9268102]
29. Scheuner MT, McNeel TS, Freedman AN. Population prevalence of familial cancer and common hereditary cancer syndromes. The 2005 California Health Interview Survey. *Genet Med*. 2010; 12:726–735. [PubMed: 20921897]
30. U.S. Preventive Services Task Force (USPSTF). Recommendations on screening for ovarian cancer. [online] [cited September 7, 2005], 2010. Available at: <http://www.ahrq.gov/clinic/3rduspstf/ovariancan/ovcanrs.htm#clinical>
31. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. *JAMA*. 1997; 277:997–1003. [PubMed: 9091675]
32. Burke W, Petersen G, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. *JAMA*. 1997; 277:915–919. [PubMed: 9062331]
33. NIH Consensus Conference. Ovarian cancer. Screening treatment, and follow-up. NIH Consensus Development Panel on Ovarian Cancer. *JAMA*. 1995; 273:491– 497. [PubMed: 7837369]

34. Watson P, Narod SA, Fodde R, et al. Carrier risk status changes resulting from mutation testing in hereditary non-polyposis colorectal cancer and hereditary breast-ovarian cancer. *J Med Genet.* 2003; 40:591–596. [PubMed: 12920070]
35. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med.* 2010; 12:93–104. [PubMed: 20084010]
36. American Cancer Society. Cancer prevention & early detection facts & figures 2007. Atlanta: American Cancer Society; 2007. Available at: http://www.cancer.org/downloads/STT/CPED_2008.pdf
37. NIH State-of-the-Science Conference. [Accessed March 29, 2010.] Enhancing use and quality of colorectal cancer screening. 2010. Available at: <http://consensus.nih.gov/2010/colorectal.htm>
38. Holden, D.; Harris, R.; Porterfield, D., et al. Prepared by the RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-1. 2010 Evidence Report/Technology Assessment No. 190. Rockville, MD: Agency for Healthcare Research and Quality; Enhancing the Use and Quality of Colorectal Cancer Screening. Evidence Report/Technology Assessment No. 190. AHRQ Publication No. 10-E-002
39. Sweet KM, Bradley TL, Westman JA. Identification and referral of families at high risk for cancer susceptibility. *J Clin Oncol.* 2002; 20:528–537. [PubMed: 11786583]
40. O'Neill SM, Peters JA, Vogel VG, Feingold E, Rubinstein WS. Referral to cancer genetic counseling: are there stages of readiness? *Am J Med Genet C Semin Med Genet.* 2006; 142C:221–231. [PubMed: 17068804]
41. Prochaska JO, Velicer WF, Rossi JS, et al. Stages of change and decisional balance for 12 problem behaviors. *Health Psychol.* 1994; 13:39–46. [PubMed: 8168470]
42. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot.* 1997; 12:38–48. [PubMed: 10170434]
43. Edwards A, Unigwe S, Elwyn G, Hood K. Effects of communicating individual risks in screening programmes: Cochrane systematic review. *BMJ.* 2003; 327:703–709. [PubMed: 14512475]
44. Edwards AG, Evans R, Dundon J, Haigh S, Hood K, Elwyn GJ. Personalised risk communication for informed decision making about taking screening tests. *Cochrane Database Syst Rev.* 2006; CD001865. [PubMed: 17054144]
45. Feero WG, Bigley MB, Brinner KM. New standards and enhanced utility for family health history information in the electronic health record: an update from the American Health Information Community's Family Health History Multi-Stakeholder Workgroup. *J Am Med Inform Assoc.* 2008; 15:723–728. [PubMed: 18755994]
46. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ.* 2005; 330:765. [PubMed: 15767266]

Appendix

The Family Healthware Impact Trial (FHITr) Group consists of the following collaborators.

From the Centers for Disease Control and Prevention: Paula W. Yoon, ScD, MPH; Rodolfo Valdez, PhD; Margie Irizarry-De La Cruz, MPH; Muin J. Khoury, MD, PhD; Cynthia Jorgensen, DrPH.

From the Veterans Administration Greater Los Angeles Healthcare System: Maren T. Scheuner, MD, MPH.

From NorthShore University HealthSystem, Evanston, IL: Wendy S. Rubinstein, MD, PhD, Co-Principal Investigator; Suzanne M. O'Neill, MA, MS, PhD, Co-Principal Investigator; Nan Rothrock, PhD; Jennifer L. Beaumont, MS; Shaheen Khan, MS, MBA, MPH; Dawood Ali, MS.

From the University of Michigan: Mack T. Ruffin IV, MD, MPH, Principal Investigator; Donald Nease, MD.

From Case Western Reserve University, University Hospitals Case Medical Center: Louise S. Acheson, MD, MS, Principal Investigator; Stephen J. Zyzanski, PhD; Georgia L. Wiesner, MD; James Werner, PhD.

From Boston University School of Public Health: Catharine Wang, PhD, MSc.

From the American Academy of Family Physicians' National Research Network: Wilson D. Pace, MD, Principal Investigator; James M. Galliher, PhD; Elias Brandt, BS, BA.

From the University of Illinois at Chicago: Erin J. Starzyk, MPH.

From the University of Rochester: Robert Gramling, MD, DSc.

Table 1

Family Healthware Study: Examples of breast cancer prevention messages for a woman >40 years old who reported not having had a mammogram in the past year: Control message and personalized messages for Weak and Strong familial risk

Control Message	<p>Breast Cancer Screening:</p> <p>For women, talk to your health professional about a breast exam and when to get breast cancer screening.</p> <ul style="list-style-type: none"> A clinical breast exam is a breast cancer screening test that may help detect breast cancer early, when it is most treatable. Clinical breast exams are used in combination with mammograms when you reach age 40 and older.
Personalized Messages	
WEAK Familial Risk	<p>The impact of your family history on Breast Cancer risk is WEAK (indicated in green)</p> <p>Breast Cancer Screening: [Same as Control message above, plus:] Talk to your health professional about breast cancer screening tests, and when and how often you should be screened.</p>
STRONG Familial Risk	<p>The impact of your family history on Breast Cancer risk is: STRONG. (indicated in red).</p> <p><u>Why your family history is a risk factor:</u></p> <ul style="list-style-type: none"> (specific family history features, e.g., family members with breast cancer at a young age). Some inherited forms of breast and ovarian cancer are more common in Ashkenazi Jewish families. <p><u>The following can help reduce your overall risk:</u></p> <p>Screening Tests:</p> <p>Schedule breast cancer screening today.</p> <p>Talk to your health professional about your family history, how it affects your breast cancer risk, and your options for screening and prevention.</p> <ul style="list-style-type: none"> Mammograms and clinical breast exams are screening tests that help detect breast cancer early, when it is most treatable. There are also other ways to screen for and prevent breast cancer among women with the highest risk. <p>Learn more about breast cancer screening tests ...</p> <ul style="list-style-type: none"> <u>Clinical breast exams</u> may lead to early detection of breast cancer, especially in combination with mammogram for women age 40 and older. Schedule an appointment to have a clinical breast exam every year. Make an appointment for a mammogram every year. Mammogram can lead to early detection of breast cancer. <p>Talk to your doctor about your breast cancer risk. Because of your family history, your doctor might suggest other screening tests.</p> <p>Talk to your health professional about your risk of breast cancer, the tests that are best for you, and how often you should be screened.</p> <p>Additional Risk assessment:</p> <p>Your health professional may suggest additional steps to assess your risk, which might include <u>specialized tests, a genetic evaluation, or genetic testing.</u></p>

Table 2

Screening adherence definitions

	Average risk	Moderate risk	Strong risk
Colon	Age 50 years, fecal occult blood testing in last year or flexible sigmoidoscopy in last 5 years or colonoscopy in last 10 years	Age 40 years, fecal occult blood testing in last year or flexible sigmoidoscopy in last 5 years or colonoscopy in last 10 years	Age 30 years, colonoscopy in last 5 years
Mammogram	Women, age 40 years, in the last year	Women, age 40 years, in the last year	Women, age 20 years, in the last year
Clinical breast examination	Women, age 40 years, in the last 2 years	Women, age 40 years, in the last 2 years	Women, age 20 years, in the last year

Table 3

Demographics of study participants by study arm at baseline

Characteristics	Intervention arm (<i>N</i> = 2364), <i>N</i> (%)	Control arm (<i>N</i> = 1422), <i>N</i> (%)
Female gender	1676 (71)	962 (68)
Age (SD)	50.3 (8.4)	51.1 (8.0)
Hispanic or Latino	58 (2)	29 (2)
Race		
White or Caucasian	2134 (90)	1320 (93)
Black or African American	87 (4)	35 (3)
Asian	70 (3)	31 (2)
Other	42 (1.8)	20 (1.4)
More than one race	31 (1.3)	16 (1.1)
Marital status		
Single, never married	203 (9)	96 (7)
Married/living with partner	1857 (79)	1135 (80)
Separated/divorced	260 (11)	160 (11)
Widowed	44 (2)	31 (2)
Annual household income ^a		
<\$25,000	91 (4)	41 (3)
\$25,001–\$35,000	102 (5)	45 (4)
\$35,001–\$50,000	218 (11)	106 (8)
\$50,001–\$75,000	402 (19)	228 (18)
>\$75,000	1262 (61)	834 (67)
Currently has health insurance	2276 (96)	1380 (97)

^aTwelve percent not reported in either group.

Table 4

Family history based risk levels for colon, breast, and ovarian cancers

	Intervention (N = 2077)			Control (N = 1206)			P ^a
	Weak	Moderate	Strong	Weak	Moderate	Strong	
Colon cancer	1795 (86)	235 (11)	47 (2)	1029 (85)	141 (12)	36 (3)	0.283
Breast cancer	1605 (77)	271 (13)	201 (10)	954 (79)	132 (11)	120 (10)	0.349
Ovarian cancer	1880 (91)	112 (5)	85 (4)	1094 (91)	69 (6)	43 (4)	0.662

Data represent number (%) for each familial risk category by level and study arm for N = 3283 subjects after exclusions. Note that men are included in assessment of breast cancer and ovarian cancer risk because risk is familial and may be also pertinent to their relatives.

^aThe comparisons of proportions for each familial risk category are between study arms and are adjusted for practice clustering and site differences.

Table 5

Number of participants eligible for screening, according to familial risk category, and percent already adherent at baseline^a

Colon cancer screening				
Familial colon cancer risk category	Screening recommended for people at average risk		Additional participants eligible for screening because of increased familial colon cancer risk ^b	
	N Eligible	% Adherent ^c	N Eligible	% Adherent
Weak	1584	78	—	—
Moderate	239	88	110	45
Strong	48	88	35	37
Total	1871	79	145	43
Breast cancer screening: Mammograms ^d				
Familial breast cancer risk category	Screening recommended for women at average risk		Additional participants eligible for screening because of strong familial breast cancer risk ^e	
	N Eligible	% Adherent ^c	N Eligible	% Adherent
Weak	1532	74	—	—
Moderate	289	82	—	—
Strong	218	77	24	17
Total	2039	76	24	17

^aBaseline data on screening shown for intervention and control groups combined, as they did not differ on adherence ($P = 0.98$ for colon cancer screening, $P = 0.32$ for breast cancer screening, using generalized estimating equations in logistic regression models adjusted for practice-level clustering and risk category). Eligibility for cancer screening was assessed among 3283 participants.

^bFor example, people at moderate familial risk were eligible for colon cancer screening at age 40 or 10 years younger than the earliest age at diagnosis of colon cancer in the family, instead of starting at age 50 years.

^cAdherence to colon cancer and breast cancer screening recommended for the general population was significantly greater for people at increased familial risk ($P = 0.01$).

^dData on clinical breast examinations are not shown; 96% of women in intervention and control groups were up-to-date with clinical breast examinations at baseline and 97% at follow-up.

^eMammograms were recommended for women younger than 40 years only in the strong familial risk category. All women older than 40 years received similar mammography recommendations.

Table 6Change in colon cancer and breast cancer screening adherence by risk level^a

	Intervention (% improved)	Control (% improved)	OR (95% CI)	P	Power
Colon cancer screening (<i>N</i> = 472 participants who were not adherent to risk-appropriate screening at baseline)					
Strong CC risk	5/14 (36)	3/14 (21)	1.9 (0.5–7.2)	0.33	0.07
Moderate CC risk	9/55 (16)	6/33 (18)	0.9 (0.3–3.1)	0.86	0.06
Weak CC risk	90/222 (40)	58/134 (43)	0.9 (0.6–1.6)	0.77	0.09
Overall (adjusted for risk)	104/291 (36)	67/181 (37)	0.9 (0.6–1.4)	0.77	0.06
Mammographic screening (<i>N</i> = 515 female participants who were not adherent to risk-appropriate screening at baseline)					
Strong BC risk	27/45 (60)	17/26 (65)	0.8 (0.3–2.2)	0.65	0.08
Moderate BC risk	22/35 (63)	10/17 (59)	0.7 (0.4–1.4)	0.28	0.07
Weak BC risk	157/272 (58)	77/120 (64)	1.0 (0.6–1.6)	0.92	0.20
Overall (adjusted for risk)	206/352 (59)	104/163 (64)	0.9 (0.6–1.5)	0.82	0.19

^aUnadjusted odds ratios except where noted for overall analyses.