Evaluation of Hereditary Risk in a Screening Mammography Population

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Abstract

PURPOSE: *BRCA1* and *BRCA2* mutations significantly increase a women's lifetime risk of breast and ovarian cancer. Because several management options have shown promise in decreasing morbidity and mortality for these women, identifying potential mutation carriers is increasingly important. We developed a large-scale method to collect family histories in a population of unaffected women presenting for mammography. We then applied current risk-assessment models to determine the prevalence of women at risk for hereditary breast and ovarian cancer. MATERIALS AND METHODS: We performed a retrospective review of family histories using data collected on all unaffected women presenting for mammography over a 14-week period. The Claus, Myriad II, and Hartmann models for hereditary risk assessment were applied to the survey results. RESULTS: Five thousand seven hundred thirty-six women completed the questionnaire, of whom 695 with a personal history of breast or ovarian cancer were excluded. Family histories of the remaining 5,041 women were evaluated. Totals of 5.9%, 5.2%, and 3.3% of patients, respectively, met criteria for increased risk according to the Hartmann, Myriad II, and Claus models, corresponding to 3.5, 3.1, and 1.9 patients per day. Although 9.2% of patients met criteria for ≥ 1 model, only 1.4% met criteria for all 3. CONCLUSIONS: Application of available models to a screening population classifies a larger than expected number of women at high risk for a *BRCA1* or *BRCA2* mutation. New approaches to risk assessment and counseling are needed to apply our knowledge of hereditary risk to a broad population in a practical manner.

Clinical Breast Cancer, Vol. 6, No. 1, ???-???, 2005
Key words: *BRCA1, BRCA2,* Hereditary breast cancer, Hereditary ovarian cancer, Risk assessment

Introduction

The presence of *BRCA1* and *BRCA2* mutations are estimated to increase a woman's lifetime breast cancer risk to 50%-80% and the lifetime ovarian cancer risk to 10%-40%.[1] Data are accumulating in support of several management options for these women, including intensified screening, chemoprevention, bilateral prophylactic mastectomy, and prophylactic oophorectomy. Identifying potential mutation carriers is therefore important to potentially decrease the morbidity and mortality of cancer in these individuals.

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Submitted: ???; Revised: ???; Accepted: ???

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There is evidence that bilateral prophylactic mastectomy significantly decreases the incidence of breast cancer in *BRCA1* and *BRCA2* mutation carriers. Meijers-Heijboer et al prospectively followed 139 mutation carriers.[2] Eight of 63 patients under surveillance developed breast cancer, whereas no cases of breast cancer occurred among 76 women who underwent prophylactic surgery (P = 0.003; hazard ratio, 0). Two recent studies have shown significant benefit of prophylactic salpingo-oophorectomy in reducing ovarian cancer incidence in *BRCA1* and *BRCA2* mutation carriers. Kauff et al reported 170 women with *BRCA* mutations followed prospectively for a mean of 24.2 months.[3] Ninety-eight women underwent prophylactic surgery, and the hazard ratio for *BRCA*-associated gynecologic cancers was 0.15. Rebbeck et al reported on 551 mutation carriers identified retrospectively and prospectively.[4,5] Two hundred

Table 1 Patients Meeting Criteria for Each Model*

Model	Patients Meeting Criteria	Patients Studied
Myriad II	263	5.2%
Hartmann	295	5.9%
Claus	168	3.3%

*Patients may be counted more than once.

Table 2 Overlap Among Patients Meeting Criteria for Each Model

Model	Patients Meeting Criteria	Patients Studied
Myriad II	112	2.2
Hartmann	114	2.3
Claus	50	1.0
Myriad II and Hartmann	72	1.4
Myriad II and Claus	9	0.2
Hartmann and Claus	39	0.8
Myriad II, Hartmann, and Claus	70	1.4
Total	466	9.2

fifty-nine women followed for a mean of 6.2 years after prophylactic surgery had a hazard ratio of 0.04 for the development of coelomic epithelial cancer. Prophylactic oophorectomy also appears to reduce the incidence of breast cancer in *BRCA* mutation carriers, particularly before menopause. Data on the effect of tamoxifen use in *BRCA* mutation carriers are still preliminary. In a retrospective analysis from the Hereditary Breast Cancer Clinical Study Group, tamoxifen reduced the risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers.[6] In a subgroup analysis from the National Surgical Adjuvant Breast and Bowel Project P-1 Breast Cancer Prevention Trial, however, tamoxifen appeared to decrease breast cancer incidence among *BRCA2* mutation carriers but not among *BRCA1* mutation carriers.[7] Therefore, tamoxifen use in this population appears useful for risk reduction in *BRCA2* mutation carriers but its effectiveness in *BRCA1* mutation carriers requires further clarification.

For these strategies to have a significant impact, women at risk of having a *BRCA1* or *BRCA2* mutation must be identified in large numbers before they develop cancer. However, the best methods for identifying these individuals at high risk and the criteria to quantify their risk have not yet been agreed upon. Several models have been developed to aid in breast cancer risk assessment. The earliest of these, the Gail and Claus models, were based on correlation between risk factor data and breast cancer rates in large databases of women. The Gail model used detailed data collected on 284,780 women who participated in the Breast Cancer Detection Demonstration Project. This model incorporates family history of breast cancer in first-degree relatives, menstrual history, reproductive history, and history of benign breast disease.[8] The Claus model was developed from data from the Cancer and Steroid Hormone study conducted by the Center for Disease Control in 4730 patients and 4688 control subjects.[9] The Claus model provides age-specific lifetime estimates of breast cancer risk based on a family history of breast cancer and age at diagnosis in as many as 2 relatives.

After identification of the *BRCA1* and *BRCA2* genes, additional models were developed based on correlations between the results of genetic testing and the family histories of the women tested. These include the Couch,[10] Shattuck-Eidens (Myriad I),[11] and Frank (Myriad II)[12] models. BRCAPRO is a computer-based model that uses Bayesian analysis based on published breast and ovarian cancer incidence and penetrance rates to estimate hereditary risk.[13] The Hartmann model was based on known risk factors for *BRCA* mutations to enable a retrospective analysis of women who underwent bilateral prophylactic mastectomy at the Mayo Clinic.[14] Finally, Myriad Genetics Laboratories, Inc., posts recommendations when to perform genetic testing on its Web site.[15]

Currently, only patients with compelling risk factors are referred for genetic risk assessment and only if they or their providers recognize that risk. Various models are then applied to quantify the patient's risk and to assist in the decision of whether to recommend testing. The models listed herein are useful in the setting of a risk-assessment clinic but have not yet been applied to a screening population for breast or ovarian cancer. We applied 3 of these models (Myriad II, Hartmann, and Claus) to a population of women without cancer to determine their utility as screening tools for women at risk of hereditary breast and ovarian cancer and to determine the prevalence of high risk in that population.

Materials and Methods

With institutional review board approval, we performed a retrospective review of data collected on all unaffected women presenting for mammography at the Massachusetts General Hospital Avon Comprehensive Breast Center over a 14-week period from May 12 to August 18, 2003. Patients with a personal history of breast or ovarian cancer were excluded. Patients routinely completed a 35-item self-administered scan-compatible questionnaire that included information on personal cancer history, family history of breast or ovarian cancer, and Ashkenazi Jewish ancestry (Appendix 1). The age range (< 35, 36-39, 40-50, and > 50 years) at diagnosis for every family member with breast or ovarian cancer was solicited. Bilateral breast cancer was not captured by this form. All forms were immediately scanned into a Microsoft Access database and the information was available to clinicians the same day for patient care. We analyzed the data collected over the 14-week period using de-identified information.

We identified 3 models to evaluate hereditary risk of

Table 3 Myriad II Criteria Associated with > 10% Risk of Mutation in Patients Without Cancer[12]

Original Criteria
Non-Ashkenazi: breast cancer at age < 50 in ≥ 2 relatives, no ovarian cancer
Non-Ashkenazi: breast cancer at age < 50 and ovarian cancer at any age
Ashkenazi: breast cancer at age < 50 years in 1 relative, no ovarian cancer
Ashkenazi: breast cancer at age < 50 years in ≥ 2 relatives, no ovarian cancer
Ashkenazi: ovarian cancer any age in 1 relative, no breast cancer at age < 50 years
Ashkenazi: ovarian cancer any age in ≥ 2 relatives, no breast cancer at age < 50 years
Ashkenazi: breast cancer at age < 50 years and ovarian cancer at any age
Modified Criteria
Non-Ashkenazi plus breast cancer at age ≤ 50 years in ≥ 2 relatives*
Non-Ashkenazi plus breast cancer at age ≤ 50 in 1 relative plus ovarian cancer at any age*
Ashkenazi plus breast cancer at age ≤ 50 years in 1 relative
Ashkenazi plus ovarian cancer at any age in 1 relative

*Same bloodline.

Figure 1 Patients Meeting Criteria of Each Model

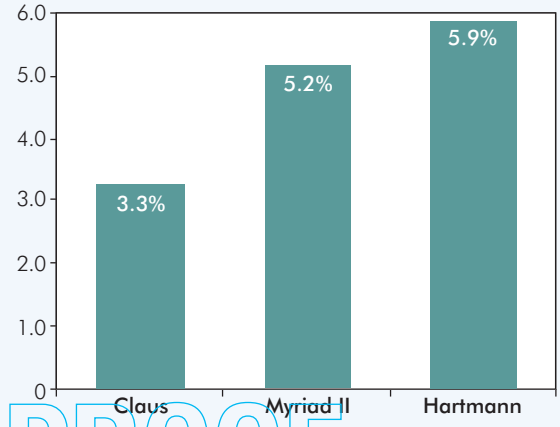
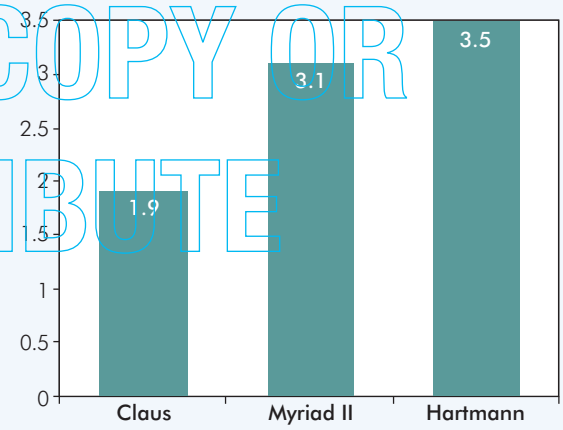


Figure 2 Risk Assessment Referrals per Day



breast and ovarian cancer that were appropriate for use as screening tools in women without cancer (Tables 1-4)[9,12]: the Claus model, the Frank (Myriad II) model, and the Hartmann model. Criteria from each model associated with a 10% risk of mutation or a 21% lifetime risk of breast cancer were used. A 10% risk of mutation was chosen according to the 1996 American Society of Clinical Oncology guidelines for genetic testing referral[16] and used for the Frank model, in which risk factors are associated with a prevalence or risk of a *BRCA* mutation. The Claus criteria provide a lifetime risk of breast cancer development rather than risk of mutation carrier status, and a 21% lifetime risk threshold (an approximate doubling of the lifetime risk) was used.[17,18] The Hartmann model is divided into high-risk and moderate-risk groups; we used the high-risk criteria.

Given variation in data elements in various models, including age ranges, the selected criteria were then modified to conform to our available data. Specifically, the age ranges were changed from < 50 years to ≤ 50 years in the Myriad and Claus models, with additional age adjustments for the Claus model, as we did not have an age breakdown for women > 50 or < 36 years of age. We eliminated the criterion for bilateral breast cancer from the Hartmann model, potentially missing a small number of women, and changed the age in one of the Hartmann criteria from < 45 years to ≤ 50 years. Overall, these changes may be expected to slightly increase the number of women considered to be at high risk. Initial and modified model criteria are listed in Tables 3, 4, and 5.[9,12,14] The database was queried to determine the number of women who met these modified criteria for each model and combination of models. The average number of patients meeting criteria per day was calculated using the average number of women without cancer undergoing mammography per day at the Avon Comprehensive Breast Center.

Results

From May 12 to August 18, 2003, 5,736 women completed the questionnaire, of whom 695 with a personal history of breast or ovarian cancer were excluded. Family histories of the remaining 5,041 women (an average of 60 per day) were evaluated according to the modified criteria for each model. Totals of 5.9% and 5.2% of patients met the Hartmann and Myriad II criteria, respectively, and 3.3% of patients met the Claus criteria (Figure 1). This corresponds to an average of 3.5, 3.1, and 1.9 patients per day for the Hartmann, Myriad II, and Claus models, respectively (Figure 2). Four hundred sixty-six patients, or 9.2% of patients studied, met the

Table 4 Claus Criteria Associated with > 21% Lifetime Risk of Breast Cancer[9]

Original Criteria
1 first-degree relative with breast cancer at age < 30 years
1 first-degree relative with breast cancer at age < 40 years, 1 first-degree relative with breast cancer at age < 80 years
1 first-degree relative with breast cancer at age < 50 years, 1 first-degree relative with breast cancer at age < 70 years
2 first-degree relatives with breast cancer at age < 60 years
Mother with breast cancer at age < 40 years, maternal aunt with breast cancer at age < 80 years
Mother with breast cancer at age < 50 years, maternal aunt with breast cancer at age < 70 years
Mother with breast cancer at age < 60 years, maternal aunt with breast cancer at age < 60 years
Mother with breast cancer at age < 70 years, maternal aunt with breast cancer at age < 50 years
Mother with breast cancer at age < 80 years, maternal aunt with breast cancer at age < 40 years
Mother with breast cancer at age < 30 years, paternal aunt with breast cancer at age < 70 years (< 80 years = 21.0%)
Mother with breast cancer at age < 50 years, paternal aunt with breast cancer at age < 30 years
1 second-degree relative with breast cancer at age < 30 years, 1 second-degree relative with breast cancer at age < 70 years*
1 second-degree relative with breast cancer at age < 40 years, 1 second-degree relative with cancer at age < 50 years*
Modified Criteria
1 first-degree relative with breast cancer at age < 36 years
1 first-degree relative with breast cancer at age < 50 years plus 1 first-degree relative with breast cancer any age
2 first-degree relatives with breast cancer at age < 50 years
Mother with breast cancer at age < 50 years plus maternal aunt with breast cancer at any age
Mother with breast cancer any age plus maternal aunt with breast cancer at age < 50 years
Mother with breast cancer at age < 36 years plus paternal aunt with breast cancer at any age
Mother with breast cancer at age < 50 years plus paternal aunt with breast cancer at age < 36 years
1 second-degree relative with breast cancer at age < 36 years plus 1 second-degree relative with breast cancer at any age*
1 second-degree relative with breast cancer at age < 40 years plus
1 second-degree relative with breast cancer at age < 50 years*

*Same bloodline.

criteria for ≥ 1 model (Table 2). Seventy patients (1.4%) met the criteria for all 3. Only 15% of patients who met criteria for ≥ 1 model met the criteria for all 3. Although the numbers of women identified may be slightly higher than if we had not modified the criteria, our changes would not be expected to affect the overlap among models.

Table 5 Hartmann High-Risk Criteria[14]

Original Criteria
≥ 2 first-degree relatives with breast cancer
1 first-degree relative plus ≥ 2 second- or third-degree relatives with breast cancer
1 first-degree relative with breast cancer at age < 45 years plus 1 other relative with breast cancer
1 first-degree relative with breast cancer plus ≥ 1 relatives with ovarian cancer
2 second- or third-degree relatives with breast cancer plus ≥ 1 relative with ovarian cancer
1 second or third-degree relative with breast cancer plus ≥ 2 relatives with ovarian cancer
≥ 3 second- or third-degree relatives with breast cancer
1 first-degree relative with bilateral breast cancer
Modified Criteria
≥ 2 first-degree relatives with breast cancer
1 first-degree relative plus ≥ 2 second- or third-degree relatives with breast cancer*
1 first-degree relative with breast cancer at age < 50 years plus 1 other relative with breast cancer*
1 first-degree relative with breast cancer plus ≥ 1 relative with ovarian cancer*
2 second or third-degree relatives with breast cancer plus ≥ 1 relatives with ovarian cancer*
1 second or third-degree relative with cancer plus ≥ 2 relatives with ovarian cancer*
≥ 3 second- or third-degree relatives with breast cancer*

*Same bloodline.

Discussion

In this retrospective data analysis, 3.3%-5.9% of women without breast or ovarian cancer undergoing mammography were found to be at risk for hereditary *BRCA1* or *BRCA2* mutations by ≥ 1 of 3 accepted models, and 9.2% were found to be at risk when all 3 models were used. These results are similar to the findings of Hughes et al, who found a 6% prevalence of family histories suspicious for hereditary breast and ovarian cancer in a primary care practice with use of broad criteria followed by pedigree review by a surgical oncologist experienced in risk assessment.[19]

Further evaluation reveals surprisingly little overlap among patients meeting the criteria for each model (Table 2). Although 9.2% of patients met criteria for ≥ 1 model, only 1.4% met criteria for all 3. For patients who met the Myriad II or Hartmann criteria, 27% and 24%, respectively, met the criteria for the other. Among patients who met the Claus criteria, 5% and 23% met criteria for the Myriad II and Hartmann models, respectively. Therefore, choosing the appropriate model for screening for hereditary risk is more complicated than determining the desired sensitivity; use of any one of these models alone may miss large numbers of women at risk.

Several models were not used for various reasons. The Gail model underestimates the risk of breast cancer in women with hereditary mutations and is not appropriate for evaluation of hereditary risk.[20] The Couch model describes the risk of a *BRCA1* mutation among women with breast cancer and is therefore not applicable to a screening population, nor does it address *BRCA2*. The Myriad I model was designed in a similar fashion. BRCAPRO, although considered a highly accurate tool for risk assessment, requires a significant amount of time for data entry and was believed to be impractical for large-scale screening. It is best applied to selected patients at very high risk, perhaps as a second-stage screen for women identified by the aforementioned criteria. The online Myriad recommendations for risk assessment include screening of anyone with a relative who has had breast cancer before the age of 50 and were believed to be too broad for useful screening.

Generally, risk assessment and counseling requires 1-2 hours for the initial visit plus additional visits if genetic testing is elected. Using our current approach to counseling, it would take tremendous resources to manage the number of women identified in our mammography program who should be referred for risk assessment. Based on the data presented, there is not a single model on which we can base calculations of the resources necessary to meet the needs of these women. A single reliable model would allow more definitive calculation of number of women at high risk and would facilitate calculation of the required resources. Considering that women < 40 years of age generally do not undergo mammography, the number of women at risk would be expected to increase if screening for a *BRCA1* or *BRCA2* mutation were applied to a broader population than we have reported.

Conclusion

Breast cancer risk assessment is becoming increasingly important, as we are better able to provide risk-reduction therapies. We developed a system to collect family histories in the course of screening mammography, and, with modifications of currently available models, were able to identify a large number of women who need risk assessment. The problem the medical community must now address is how to manage this immense population and/or find ways to decrease the number of women considered to be at high risk. We need to develop an accurate and focused model that would allow more precise identification of those at risk. Risk assessment resources could then be directed to a smaller number of women. However, this is not an easy task. BRCAPRO, the computerized model currently used in many high-risk clinics, comes closest in terms of accuracy, but, as currently used, is inappropriate for screening. In addition, we need to develop new approaches to risk assessment and counseling that are simpler and more efficient. More women could then undergo risk assessment, with remaining resources targeted to the identified mutation carriers. This dual approach may allow us to manage the large number of women at risk. We continue to work on practical ways to identify the large numbers of women potentially at risk for hereditary breast and ovarian cancer and to make risk assessment available to these women.

Acknowledgements

This research was supported in part by the Boston Race for the Cure, an affiliate of the Susan G. Komen Breast Cancer Foundation; the Charles E. Dana Foundation; and the Robert E. Wise Foundation.

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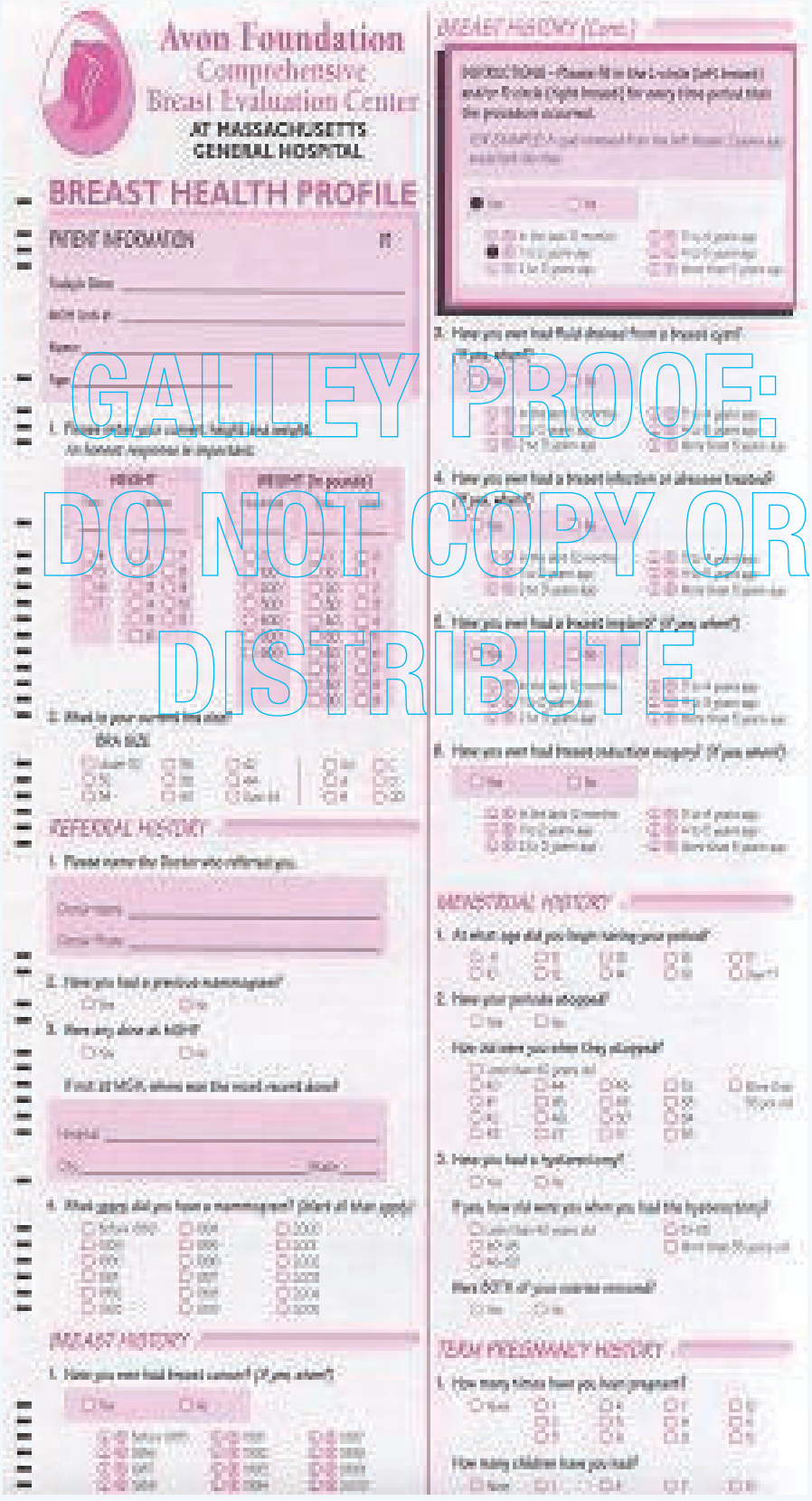
Appendix 1 Need a title for this



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BREAST HEALTH PROFILE

PATIENT INFORMATION

REFERRAL HISTORY

BREAST HISTORY

BREAST HISTORY (Cont.)

MENSTRUAL HISTORY

TEAM PREGNANCY HISTORY

Appendix 2 Need a title for this