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Significant differences among physician specialties in management recommendations of *BRCA1* mutation carriers

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Abstract

The National Comprehensive Cancer Network (NCCN) has published guidelines for hereditary breast and ovarian cancer syndrome (HBOCS) management. Little data exist on compliance with these guidelines among different physician specialties. We performed an on-line case-based survey by randomly sampling physicians from five specialties, Family Medicine (FM), Obstetrics and Gynecology (OG), General Surgery (GS), Internal Medicine (IM), and Hematology and Oncology (HO). The physicians (n = 225) were asked to provide HBOCS management of healthy women ages 40–42 in the presence of a familial *BRCA1* mutation. For women negative for the *BRCA1* mutation, 59% of the physicians recommended appropriate surveillance although with significant differences among specialties; P = 0.01. Using an aggregate screening intensity score, physicians clearly recommended more intense screening for mutation positive than negative women (P < 0.0001), but only 16% of physicians followed NCCN guidelines for *BRCA1*-positive women. Seventy-six percent of all physicians recommended breast MRI with significant variation among specialties ranging from 62% of FM to 89% of OG (P = 0.0020). Similarly, 63% of physicians recommended prophylactic oophorectomy, with 76 and 78% of GS and OG compared

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to 38% of IM ($P < 0.0001$) and 57% recommended prophylactic mastectomy ranging from 84% of HO to 32% of FM ($P < 0.0001$). Independent of specialty, respondents with BRCA testing experience recommended more intense management than those without; $P = 0.021$. Management recommendations of *BRCA1* mutation carriers are not consistent with NCCN guidelines and vary by medical specialty and genetic testing experience. Targeted education of physicians by specialty is needed, so that optimal management is offered to these high-risk women.

Keywords

BRCA1; BRCA; Surveillance; Guidelines; Physicians

Introduction

Hereditary breast and ovarian cancer syndrome (HBOCS) is associated with mutations in two known tumor suppressor genes *BRCA1* and *BRCA2*. Clinical testing for the *BRCA1* and *BRCA2* genes has been commercially available since 1995, and many thousands of women have undergone genetic testing to identify an inherited cancer predisposition. Mutation carrier status is important to determine further surveillance measures as well as management options. Recommendations for the clinical management of HBOCS are based on several key features of BRCA mutation carriers: (1) early onset of breast cancer, (2) increased risk of ovarian cancer, (3) risk of second primary breast cancer, and (4) risk for male breast cancer. Based on the best available evidence, the National Comprehensive Cancer Network (NCCN) has put forth practice guidelines for the appropriate management of *BRCA1/2* mutation positive versus *BRCA1/2* negative women (http://www.nccn.org; version 1.2010) [1] [2]. The following screening strategy for mutation-positive women is recommended for those who have not yet undergone risk-reducing surgery [3, 4].

- Monthly breast self-examination (BSE) beginning at age 18 years
- Clinical breast examination semi annually beginning at age 25 years
- Annual mammography and breast MRI screening beginning at age 25 years or individualized based on the earliest age of onset in the family
- Twice yearly ovarian cancer screening with ultrasound and serum CA-125 levels beginning at age 35 years

Benefits of risk-reduction surgeries and chemo-preventive therapies are also known and have become standard of care in the management of such patients. In both retrospective and prospective series, prophylactic mastectomy decreases the incidence of breast cancer by 90% or more in women at high risk [4, 5]. In women with *BRCA1/2* mutations, bilateral oophorectomy reduces the risk of breast as well as ovarian cancer. The NCCN guidelines with regard to risk-reducing surgeries include [1]

- Salpingo-oophorectomy, ideally between the ages of 35–40 years or upon completion of child bearing, or individualized based on earliest age of onset of ovarian cancer in the family [5, 6].
- Discussion of risk-reducing mastectomy should be carried out on a case-by-case basis.

Although these guidelines have been available for many years, it is not clear as to what extent they are followed by physicians in clinical practice or how compliance may vary among different physician specialties. In this study, we present results from a survey of practicing physicians in Texas from five different specialties. We assessed their surveillance and management recommendations in simulated cases and assessed their experience with

genetic testing in their practice. We report to what extent their recommendations were comparable to the NCCN guidelines.

Methods

Study participants and survey methods

This online survey of Texas physicians included sampling of 1000 practicing physicians from five specialties (200 physicians from each specialty were selected): Family Medicine (FM), General Surgery (GS), Internal Medicine (IM), Obstetrics and Gynecology (OG), and Hematology and Oncology (HO). Additional details about this survey are described in Plon et al. [7].

Survey instrument

The survey questionnaire consisted of four hypothetical case scenarios regarding genetic testing decisions and HBOCS cancer risk management of unaffected women ages 40–42 years in the presence of a relative affected with cancer. In this report, we focus on the two cases where healthy at-risk women were tested for the deleterious mutation in *BRCA1* found in a first degree relative with cancer. Case 2 of survey: two daughters, ages 41 and 43 years, of a woman with ovarian cancer at age 65 years who is positive for the 4229delTG mutation in the *BRCA1* gene. One daughter is found to be positive for the mutation while the other is negative. Case 4 of survey: 44-year-old daughter of a woman, who is positive for the Q1408X mutation and N810YVUS in the *BRCA1* gene. The daughter was found to be positive for Q1408X and negative for VUS and 42-year-old niece of that woman was found to be negative for both *BRCA1* changes. Only results from Case 2 are reported since the results of Case 4 were similar.

In each case the physician was provided the results of genetic testing for the at-risk relative and then asked the same set of cancer risk management questions (described below). In order to assess overall intensity of screening, we assigned a weighted score for each item. The questions and weighted score matrix are described in the Statistical analysis and Findings section.

Statistical analysis

Descriptive statistics were calculated to summarize the physicians' choices to the survey questions and their characteristics. Chi-Square test was performed to examine the difference between the physician specialties and physicians' *BRCA1/2* testing experience. As described previously [7], we generate a HBOCS management intensity score by assigning points for the screening and surgery options selected and sum the total points for each case to develop a cancer risk management intensity score. However, in this report, we limited the items included in the score (Table 1) given that CA125 and transvaginal ultrasound are only recommended for women who decline oophorectomy and mastectomy should be discussed on a case-by-case basis. Therefore, we did not include those recommendations in this analysis, yielding a maximum score of 12. Distributions of scores for averages of positive cases and negative cases are shown graphically by histogram and kernel density curves and were compared by pairwise Wilcoxon signed-rank test. The difference between the scores of positive cases and negative cases was examined by general linear model with specialty and BRCA testing experience as the factors. The interaction term of specialty and testing experience was removed from the final model because it was not significant. *P* values of less than 5% were considered significant.

Role of the funding source

NHGRI supported the faculty, staff and costs of carrying out the online survey, the $50 incentive for physicians to complete the survey, and the analysis of the data. The funders had no role in the design of the study, data analysis, and interpretation in the writing of this report or the decision to submit for publication.

Findings

Physicians were randomly selected for participation from those for whom an email address was available in the Texas Medical Association database. Invitations were mailed to 200 individuals from each specialty group, and the response rate for all five specialty group samples combined was 23%. As described previously (Table 3 in previous publication by Plon et al.), detailed demographic and practice environment data were available for both responders and non-responders. Comparisons of the two groups on nine demographic variables revealed a significant difference only in the mean years in practice (14.2 years for responders vs. 16.7 years for non-responders; Kruskal–Wallis rank sum, $P = 0.004$).

For each case, the physician was first provided the results of comprehensive *BRCA1/2* genetic testing for the relative with cancer and then provided the results of genetic testing for the healthy at-risk relative (ages 40–43) with regard to whether the at-risk relative did or did not carry the deleterious *BRCA1* mutation (test positive) found in the cancer patient. For each relative, the physicians were asked to make recommendations for management of the healthy woman's cancer risk including surveillance and prophylactic surgery.

As described in methods, we generated a limited HBOCS management intensity score by summing the assigned points for the most straightforward screening and surgery options in the NCCN guidelines; clinical breast exam, mammography, breast MRI, and prophylactic oophorectomy (Table 1). Based on NCCN guidelines, for a woman found to carry a deleterious *BRCA1* mutation, the optimal score was 10 and 4 for a non-carrier as screening is similar to general population recommendations predominantly focusing on routine annual mammography and annual clinical breast exam (Table 1).

For the healthy daughter found to be negative for the deleterious *BRCA1* mutation, 59% of the physicians recommended surveillance as set forth by NCCN (Fig. 1a). There were significant differences among specialties; only 43% of GS and HO physicians recommended appropriate surveillance compared to 75% of OG, 64% of FM, and 60% of IM (Chi-Square test, $P = 0.01$). This likely reflects that HO and GS typically manage high-risk patients.

Compared to the daughter with a negative result the intensity of screening was clearly increased for the daughter found to carry the deleterious *BRCA1* mutation with a median of 9 (range 2–12) (Wilcoxon signed-rank test, $P < 0.0001$) (Fig. 1b). However, only approximately 16% ($n = 37$) of physicians made recommendations consistent with the NCCN guidelines. Overall, IM and FM recommended less intense screening. For example, only 65% of IM and 62% of FM recommended breast MRI for mutation-positive women compared to 89% of OG and 90% of HO (Chi-Square test, $P < 0.0001$) (Fig. 2a). With regard to recommendations for prophylactic surgery 78, 77, and 76% of the GS, HO, and OG specialty groups respectively, recommended prophylactic oophorectomy compared with 38% of IM and 50% of FM (Chi-Square test, $P < 0.0001$) (Fig. 2b). Similar differences among specialties were seen for prophylactic mastectomy recommendations (Fig. 2c).

One explanation for the differences among specialties in screening recommendations may relate to the physician experience with genetic testing in their practice. After completing the questions with regard to the cases each physician was asked about whether they had ever

ordered *BRCA1/2* testing and approximately how many times in the last 6 months. IM and FM physicians were less likely to have ordered BRCA testing in their own practice (Chi-Square test, $P < 0.0001$) (Table 2). We then analyzed the management recommendations based on experience and specialty. Overall, physicians who had ordered BRCA testing in their practice recommended more intense management of mutation-positive women than those that had not (general linear model, $P = 0.021$). Regardless of testing experience, FM and IM still recommended less intense management of mutation-positive women (contrast in general linear model, $P = 0.013$). Bilateral mastectomy was recommended by 74% of physicians who had ever ordered BRCA testing compared to 47% who had never ordered the test ($P < 0.0001$) (Table 3). Similarly, 78% of physicians who had ordered BRCA testing had recommended bilateral oophorectomy compared to 54% of those that had never ordered the test ($P < 0.0001$). No significant differences in recommendations for breast MRI were found among physicians who had ordered the test versus those that had not. This demonstrates that physicians who have experience in ordering the BRCA test were also more comfortable in recommending life altering management options such as prophylactic surgeries.

Discussion

Genetic testing for *BRCA1* and *BRCA2* mutations is widely accepted as standard of care in patients with known or suspected diagnosis of HBOCS, and cancer risk management strategies have been established for mutation carriers. We surveyed Texas physicians from five specialty groups as to their recommendations for cancer risk management of unaffected women who have undergone testing for a deleterious *BRCA1* mutation found in a close family member with cancer. The response rate in this survey was low, which we understand is one limitation of this study; however, as previously described we have detailed information on both responders and non-responders and found only time in practice as significantly different [8]. The physician respondents are highly representative of the physicians in these specialty groups in the Texas Medical Association database. The respondents were clinically active physicians participating in direct patient care.

Not surprisingly physicians clearly recommended more intense cancer screening when a woman was found to carry a *BRCA1* deleterious mutation, compared to a non-carrier, consistent with the increased risk of early-onset cancer. However, when each physician response was analyzed individually, only 17% of the physicians followed all the NCCN recommendations. It is important to note that the degree of intensity was clearly a function of physician specialty. The current NCCN recommendations for breast MRI [2] have also been adopted by other organizations including the American Cancer Society who recommend annual MRI, in addition to mammography for screening women with a 20–25% or greater lifetime risk of breast cancer from the age of 30 years [3]. The National Institute for Health and Clinical Excellence has published guidelines that advocate breast MRI for those women with a strong family history or those with *BRCA1/2* mutations, as clinical breast exams and conventional imaging techniques such as mammography and breast USG are less effective in this group [9]. Thus, despite the consensus of recommendations for breast MRI as a breast cancer screening modality based on both family history and genetic testing status, it is disconcerting that a significantly lower percentage of FM and IM physicians recommended breast MRI for a *BRCA1* mutation carrier compared with other specialties. Given that FM/IM physicians often recommend breast cancer surveillance for their patients there is a need for better education on the indications for breast MRI. The FM/IM specialty groups were also less likely to recommend prophylactic salpingo-oophorectomy for mutation carriers, another NCCN recommendation.

Older studies carried out when BRCA testing was first available demonstrated that few non-geneticist physicians have discussed or ordered BRCA testing [10, 11]. As we found, oncologists are more likely than primary care specialists (IM and FM) to have discussed and/or ordered BRCA testing [12–14]. In another study, 38% of oncologists had ever ordered a BRCA test compared with only 20% of OG and 11% of IM [8]. However, it is important to note that 36% of the randomly selected physicians in this study who were surveyed in late 2008 and early 2009 had ordered *BRCA1/2* testing in their own practice. A similar survey performed by our group in late 2009 found that 43% had ordered testing (data not shown). There is clearly increased ordering of genetic testing by physicians without genetics specialty training. Physicians who have ordered the test in their practice might be assumed to be more aware and cognizant of management strategies and as shown in Table 3, breast MRI and prophylactic surgeries were recommended significantly more by physicians familiar with the test. In some cases, physicians with testing experience recommended more intense management than was recommended by the NCCN guidelines, e.g., with regard to frequency of breast MRI. Conversely among physicians without testing experience a small subset recommended surveillance of a *BRCA1*-positive woman comparable to general population recommendations.

Other studies have demonstrated that risk-reducing surgeries such as prophylactic mastectomies and salpingooophorectomies are less accepted than other interventions. In a French study of surgeons and gynecologists and obstetricians' attitudes only 10.9 and 22.9% said they would find it acceptable to recommend mastectomy and oophorectomy respectively [15]. In one US survey of surgeons, 85% of plastic surgeons compared to 47% of general surgeons and 38% of gynecologists agreed that prophylactic mastectomy had a role in the care of high-risk women [16]. Prophylactic oophorectomy is more widely accepted than mastectomy [17, 18]. We found that recommendations for prophylactic surgery are not limited to the physician groups performing the operation as GS and OG were second to HO in recommending prophylactic surgeries potentially reflecting experience and/or specialized knowledge of the HO physicians with the NCCN guidelines [19, 20].

Genetics knowledge is not uniform across medical specialties. The greatest knowledge about specific pathologies is found among physicians caring for affected persons [21]. Several studies have shown that specialists were more knowledgeable about cancer genetics than general and family practitioners [22]. Consistent with our findings on genetic testing experience, Doksum et al. [8] showed that knowledge of genetics of breast cancer was greater among oncologists who were familiar with the test compared to oncologists who had never discussed the test. On the other hand, direct to consumer marketing has increased patient awareness about HBOCS and may lead to an increasing burden on FM and IM who are faced with patient inquiries from healthy at-risk relatives of cancer patients about testing and the appropriate cancer risk-reduction strategies. This study demonstrates that these two specialty groups are likely to recommend less intense risk-reduction strategies even in the face of a *BRCA1*-positive test compared to national guidelines.

Knowledge of national guidelines and physician recommendation is important for optimal patient care. In one recent report, lack of physician recommendation was the most frequently cited reason by at-risk women for not having surveillance procedures [23]. Our study also portrays varying concordance of recommendations with NCCN guidelines among physician specialties with less intense management by FM and IM physicians and more intense cancer risk management (such as semi-annual breast MRI or mammograms) by other specialties. There is a need for a large educational effort to prepare non-geneticist physicians for the challenges as genetic testing becomes available in many different areas of medicine [24, 25]. This study highlights that there is a need to tailor this physician education to each specialty

so that educational issues can be addressed that allows the integration of genetic testing and appropriate subsequent cancer risk management into clinical practice.

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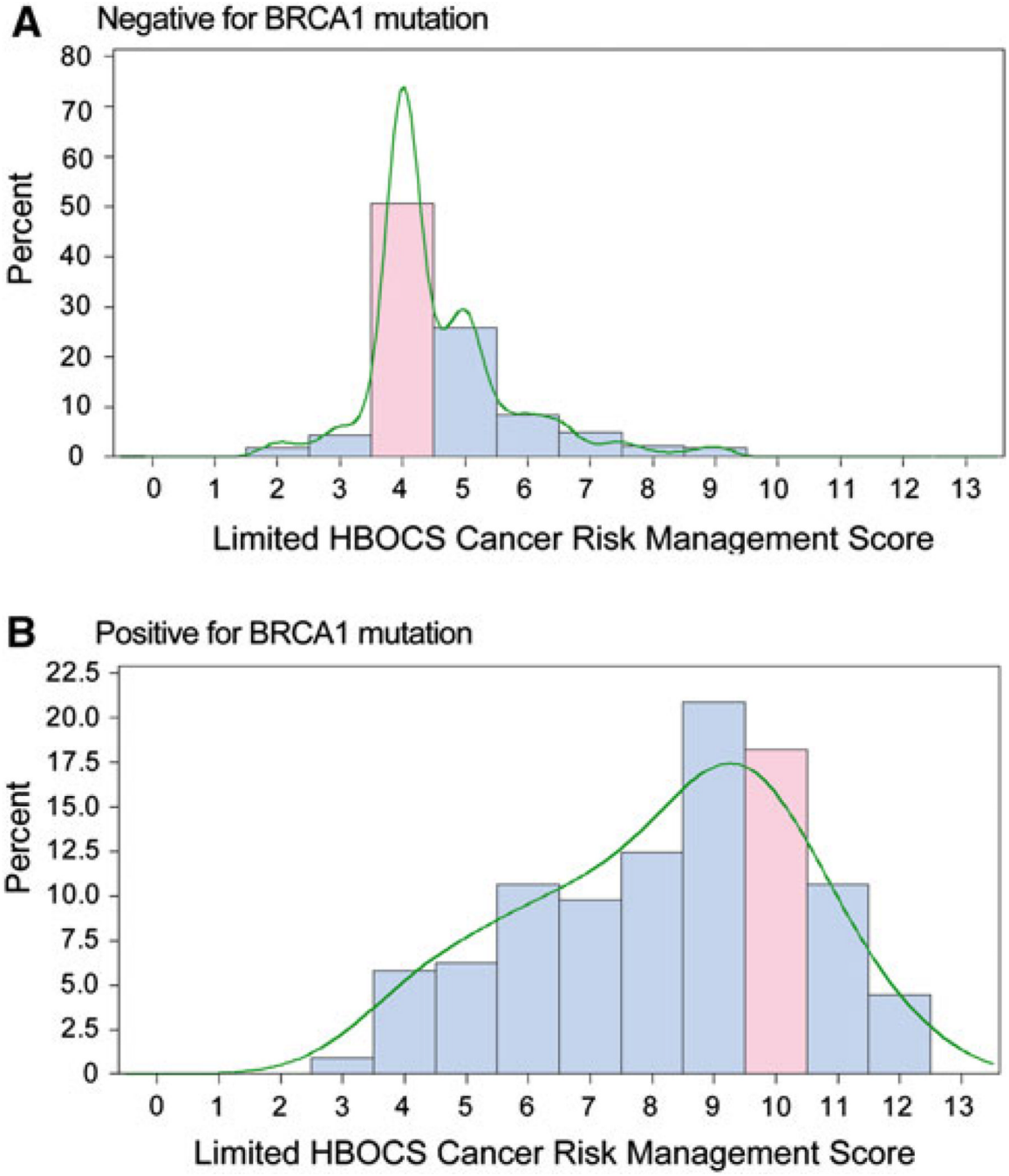

Fig. 1.

Distribution of HBOCS surveillance scores from all respondents using the weighted screening score for healthy women in their early forties who are **a** negative and **b** positive for the *BRCA1* mutation found in their mother. The score in *pink* is consistent with NCCN guidelines. The curves show the non-parametric kernel density estimation

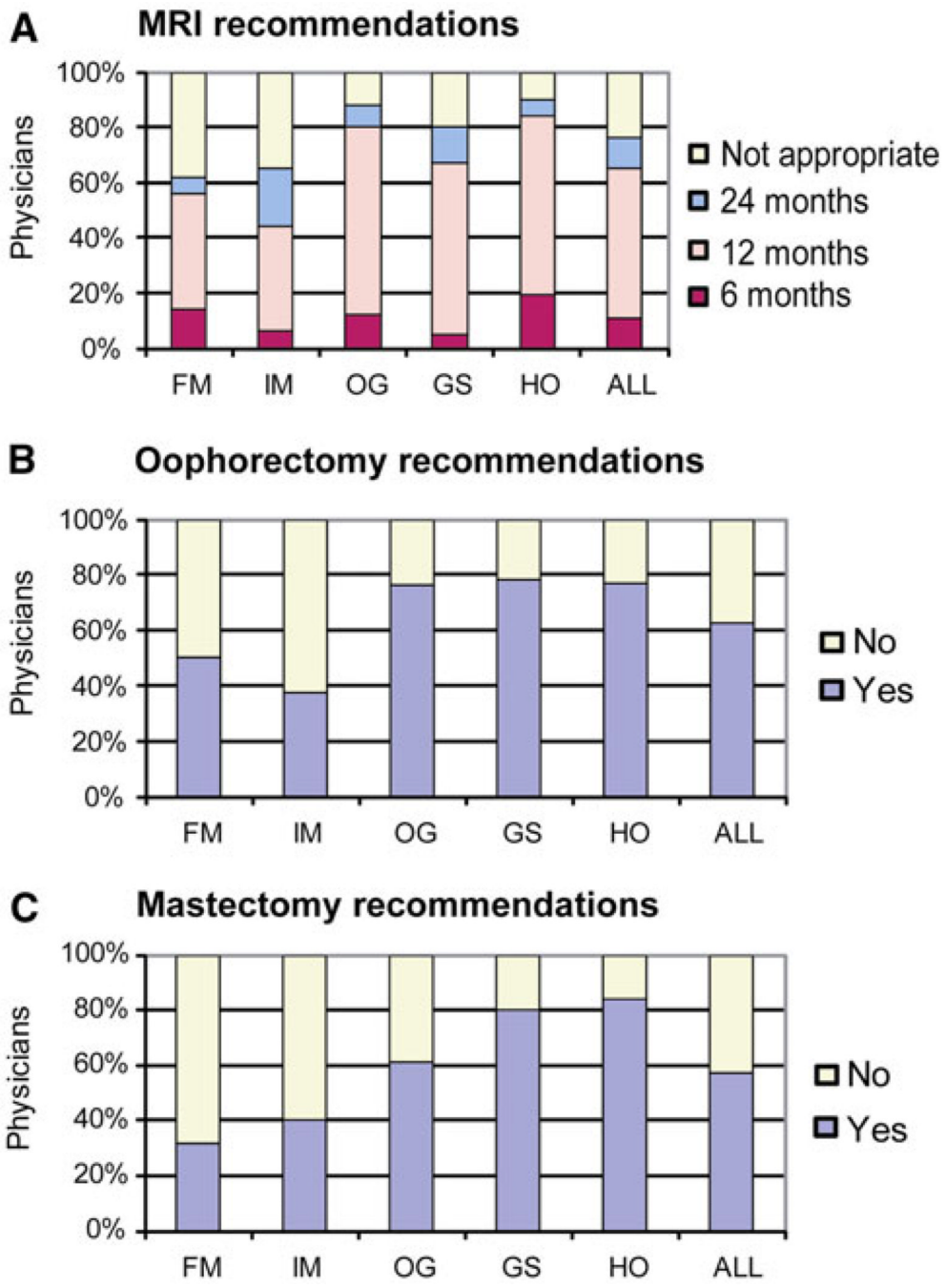

Fig. 2.

Recommendations for **a** breast MRI, **b** prophylactic salpingooophorectomy, and **c** prophylactic mastectomy for *BRCA1* mutation-positive individuals, by different specialties

Table 1

Cancer risk management questions included in the survey and the points allotted to each to generate HBOCS management intensity scores

	6 months	12 months	24 months	Not appropriate
Clinical breast exam	3	2	1	0
Mammogram	3	2	1	0
Breast MRI	3	2	1	0
	Yes	No		
Bilateral oophorectomy	3	0		
Maximal Score	12			
NCCN Score for *BRCA1* negative	4			
NCCN Score for *BRCA1* positive	10			

Table 2

Distribution of physician specialties response to question about ever having ordered *BRCA* testing

Ever ordered BRCA	FM (%)	IM (%)	OG (%)	GS (%)	HO (%)	ALL (%)	*P* value
Yes	16	10	49	36	87	36	<0.0001
No	84	90	51	64	13	64	

Table 3

Recommendations for breast MRI, prophylactic mastectomy, and prophylactic oophorectomy for *BRCA*-positive cases, based on having ever ordered the *BRCA* test versus not

	Ever ordered *BRCA1/2* testing		
	Yes (*n* = 81) (%)	**No (*n* = 144) (%)**	***P* value***
Clinical breast exam	99	98	–
Mammogram	94	96	–
Breast MRI	83	73	0.015
Bilateral mastectomy	74	47	<0.0001
Bilateral oophorectomy	78	54	<0.0001

* *P* values were calculated from Chi-square test