

A Survey among Breast Cancer Specialists on the Low Uptake of Therapeutic Prevention with Tamoxifen or Raloxifene

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Abstract

With this survey, we aimed to address the reasons why physicians are reluctant to prescribe breast cancer-preventive therapy with the selective estrogen receptor modulators (SERM) tamoxifen or raloxifene despite a strong evidence of efficacy. A self-administered 5-point Likert questionnaire was given during breast cancer meetings in Europe or sent via email to rank the importance of 10 predefined reasons for low uptake of SERMs for breast cancer therapeutic prevention. Analyses tested the associations between the stated reasons and physician characteristics such as gender, age, country of work, and specialty. Of 246 delivered questionnaires, 27 were incomplete and were excluded from analysis. Overall, there was a small variability in response scores, with a tendency for physicians to give moderate importance (score = 3) to all 10 statements. However, the top five reasons

were: the expected greater preventive effectiveness of aromatase inhibitors (70.3% with score >3), difficulty applying current risk models in clinical practice (69.9%), the lack of clarity on the most appropriate physician for prevention advice (68.4%), the lack of reliable short-term biomarkers of effectiveness (67.5%), and the lack of commercial interest in therapeutic prevention (66.0%). The lack of reliable short-term biomarkers showed a tendency to discriminate between medical oncologists and other breast specialists (OR = 2.42; 95% CI, 0.93–6.25). This survey highlights the complexity of prescribing decisions among physicians in this context. Coupled with the known barriers among eligible women, these data may help to identify strategies to increase uptake of breast cancer therapeutic prevention. *Cancer Prev Res*; 11(1); 38–43. ©2017 AACR.

Introduction

Breast cancer is the most common female tumor globally and the primary cause of cancer-related death in women worldwide (1). Preventive therapy may be crucial to reduce breast cancer burden. A meta-analysis of individual-level participant data from nine phase III trials in over 93,000 women demonstrated a preventive effect of SERMs in reducing invasive estrogen (ER)-positive breast cancer incidence by approximately 40% (2), with evidence for a 20-year carryover effect in one trial (3). Currently, two SERMs are FDA-approved drugs for primary breast cancer prevention: (i) tamoxifen for premeno-

pausal and postmenopausal women at high risk of breast cancer; and (ii) raloxifene for postmenopausal women with osteoporosis or at high risk of breast cancer. Important public agencies and scientific societies recommend that clinicians discuss or offer chemoprevention with tamoxifen or raloxifene to women at high risk for breast cancer and low risk for adverse events (4–6).

Uptake of breast cancer-preventive therapy in routine care is very low (7). Among 77 million potentially eligible women for tamoxifen and 45 million for raloxifene in the United States, only 0.03% aged 35 to 79 take tamoxifen and 0.2% aged 50 to 79 take raloxifene for preventive purpose (8). Several barriers hamper breast cancer therapeutic prevention, such as fear of side effects by the women, physician reluctance in prescribing these drugs, and lack of evidence for mortality reduction (9, 10). The physician's recommendation has been reported to play a key role in influencing women decision about chemoprevention in the United States (11). However, these data are limited, particularly outside the United States. In this survey, we questioned 246 breast cancer specialists on 10 possible reasons for the low uptake of breast cancer-preventive therapy in their clinical practice and looked at possible associations with their medical background.

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Note: Prior presentation: This work was presented orally at the ESMO 2016 Congress, Copenhagen, Denmark, October 7–11, 2016.

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doi: 10.1158/1940-6207.CAPR-17-0162

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Materials and Methods

In late 2012 and early 2013, a self-administered questionnaire was given to physicians during different breast cancer

meetings in Italy and Switzerland or was sent via email to a number of European School of Oncology alumni who had attended breast cancer courses in the past 3 years.

The questionnaire items were developed by three experts in breast cancer prevention (B. Bonanni, A. Costa, and A. DeCensi) based on recent methodology (12, 13). The questionnaire included two sections. The first was composed of four questions regarding the clinicians' age at survey, gender, country of work, and specialty background. The second was developed to measure the key dimensions underlying the low uptake in clinical practice of drugs that prevent breast cancer despite strong evidence of efficacy. To assess which, in the interviewed physician's opinion, are the most important reasons for low uptake, a closed list of 10 items assessing attitudes, beliefs, and knowledge of drugs to prevent breast cancer was developed (Table 1). Subjects were asked to answer questions using a standard 5-point Likert scale of importance. Response scores ranged from 5 to 1 as it follows: "very important," "important," "moderately important," "of little importance," and "unimportant." The Likert scale is a consolidated tool that is used in social research to measure attitudes and opinions through the use of statements (14). The study was reviewed by the Galliera Hospital Scientific Committee. No incentives were offered for participation. All responses provided by the participants were completely anonymized.

Statistical analysis

Age was categorized according to tertiles of the observed distribution, and specialties were divided into two subgroups: medical oncologists versus other clinical specialties. Life expectancy at birth (LEAB) was assumed to be a valid proxy of socioeconomic status and quality of medical care in each country (15). The degree of association between medical specialty and the other physician characteristics was assessed through the χ^2 test for independence. For each statement (S), response scores were described using mean and SD, and differences among scores were assessed through the Kruskal-Wallis nonparametric rank test.

To evaluate the relationship between response scores and the physician profile, with particular reference to medical specialty, logistic regression modeling (LR) was applied to scores dichotomized according to a cut-off value of 3: unimportant or moderately important (≤ 3) versus highly important (>3) responses. LR modeling results were expressed in terms of OR and corresponding 95% confidence interval (95% CL). Statistical significance of

each variable in each LR model was assessed using the likelihood ratio test. In all analyses, a $P < 0.05$ was considered as statistically significant. Data were analyzed using Stata statistical package version 14 (StataCorp, 2015).

Results

A total of 246 surveys were collected at different locations: 15 in Switzerland (Geneva, October 31, 2012), 104 in Italy (Savona, October 13, 2012; Meldola, April, 16, 2013; Genoa, January 11, 2013), and 127 by an online survey. A total of 27 surveys were incomplete and were excluded from analysis. Also, 52 surveys did not include items regarding physician demographic characteristics. In the 194 surveys with complete demographic information, there were 103 (53.1%) females and 91 (46.9%) males with a median age of 43 years (interquartile range, 38–53 years). A total of 134 (69.1%) physicians worked in EU countries, of which 79 in Italy (40.7%), 15 (7.7%) worked in other European (non-EU) countries, 9 (4.6%) in the United States, Japan and Israel, and 36 (18.6%) in developing countries, among whom 16 (8.3%) were from Egypt. There were 117 (60.3%) medical oncologists and 77 (39.7%) physicians with other clinical background. Among the latter, 49 (25.2%) were surgical oncologists, 11 (5.7%) radiation oncologists, and 17 (8.8%) had other medical background (pathology, internal medicine, hematology, gynecology, and genetics).

Table 2 shows the observed frequency distribution between medical specialty and age, gender, and LEAB. The medical background was not associated with age at survey ($P = 0.917$), whereas medical oncologists were more frequent in women ($P = 0.002$) and countries with longer LEAB ($P < 0.001$).

Table 3 summarizes the scores obtained by each statement in terms of mean and SDs. Only small departures from the middle score = 3 (moderately important) were observed.

Figure 1 displays the percentage of important and very important scores (4 or 5) for each statement. The top five statements were: S10, expected preventive effectiveness of aromatase inhibitors (AI; 70.3% had score >3); S5, current risk factor models are not readily available for clinical practice (69.9%); S4, lack of clarity on who is the most appropriate physician for prevention advice (68.4%); S3, lack of reliable short-term biomarkers of effectiveness (67.5%); S8, no commercial interest in chemoprevention (66.0%). Considering the small variability around the overall percentage (64.9%), however, most statements obtained similar endorsement.

Table 1. Ten-item questionnaire on the reasons why physicians are reluctant to prescribe tamoxifen or raloxifene for breast cancer therapeutic prevention

Statement	
S1	There is no evidence of a reduction in breast cancer mortality.
S2	Drugs such as tamoxifen or raloxifene can cause serious side effects, including endometrial cancer and venous thromboembolism.
S3	There are no reliable short-term biomarkers to measure efficacy such as blood pressure or cholesterol, which are used in cardiovascular preventive medicine.
S4	It is unclear as to who is the most appropriate physician to take care of women at risk for breast cancer among medical oncologists, gynecologists, family doctors and surgeons.
S5	Current composite risk factor models, such as the Gail model or the Tyrer-Cuzick model, are not readily available for clinical practice.
S6	There is little knowledge in the medical community of the efficacy of drugs such as tamoxifen, raloxifene as preventive agents.
S7	Current drugs can only prevent endocrine-responsive tumors, which can mostly be cured by surgery and adjuvant therapy.
S8	There is no commercial interest to support these treatments by drugs companies as all approved drugs are out of patent.
S9	The use of these drugs has not been approved in Europe, and its prescription outside the United States and Canada is off label.
S10	A recent trial (MAP3) has suggested that aromatase inhibitors are very active in preventing breast cancer. Confirmation in a second trial will substantially increase prescription of these agents for prevention.

Table 2. Joint distribution of medical specialty and demographic characteristics

Characteristics	Medical specialty			P
	Other medical area No. (%)	Medical oncology No. (%)	Unknown No. (%)	
Age				0.917
≤40 yrs	24 (31.2)	36 (30.8)	1 (1.9)	
41-50 yrs	26 (33.8)	35 (29.9)	0 (0)	
>50 yrs	27 (35.1)	42 (35.9)	0 (0)	
Unknown	0 (0)	4 (3.4)	51 (98.1)	
Gender				0.002
Male	49 (63.6)	42 (35.9)	0 (0)	
Female	28 (36.4)	75 (64.1)	1 (1.9)	
Unknown	0 (0)	0 (0)	51 (98.1)	
LEAB				<0.001
Lower tertile	41 (53.2)	24 (20.5)	0 (0)	
Middle tertile	16 (20.8)	25 (21.4)	0 (0)	
Higher tertile	20 (26)	67 (57.3)	1 (1.9)	
Unknown	0 (0)	1 (0.9)	51 (98.1)	
Total	77 (100.0)	117 (100.0)	52 (100.0)	246

NOTE: P value of the χ^2 test for independence.

Finally, Table 4 displays the results of 10 logistic regression models to evaluate the influence of medical oncology training relative to other breast specialties in determining the percentage of highest scores in each statement. The lack of reliable short-term biomarkers (S3) exhibited a tendency to discriminate between medical oncologists and other breast specialists, although the difference was not statistically significant (OR = 2.42; 95% CI, 0.93–6.25). Second, the fear of serious side effects (S2) seems to be more important for medical oncologists than for other breast specialists, with an OR = 1.8 (95% CI, 0.79–4.24).

Discussion

The use of breast cancer therapeutic prevention with SERMs in clinical practice is low (8) despite strong evidence for efficacy (2). As few data are available about the physicians' approach to breast cancer therapeutic prevention, we evaluated the knowledge, attitudes, and beliefs among breast cancer expert physicians of different ages, sex, specialization, and country of workplace. Our survey shows that most physicians did not score the proposed statements with strong differences, but gave an average importance to all statements with only subtle differences among the 10 reasons for low drug uptake. This highlights the complexity of prescribing behavior in this context.

Table 3. Mean scores and corresponding SDs for each statement

Statement	Mean	SD	P
S1. No mortality effect	3.1	1.2	
S2. Drugs have adverse events	3.0	1.2	
S9. Off label in EU	2.9	1.1	
S4. Unclear who is the appropriate physician	2.8	1.2	
S6. Lack of medical knowledge	2.9	1.0	0.293
S7. Prevention of curable cancers	2.9	1.3	
S3. Lack of reliable biomarkers	3.0	1.1	
S5. Risk models are difficult	2.8	1.3	
S8. Drugs have poor commercial interest	3.0	1.3	
S10. AIs better than SERMs	2.8	1.1	

NOTE: Score 5, very important; score 1, unimportant; P value with the Kruskal-Wallis nonparametric rank test.

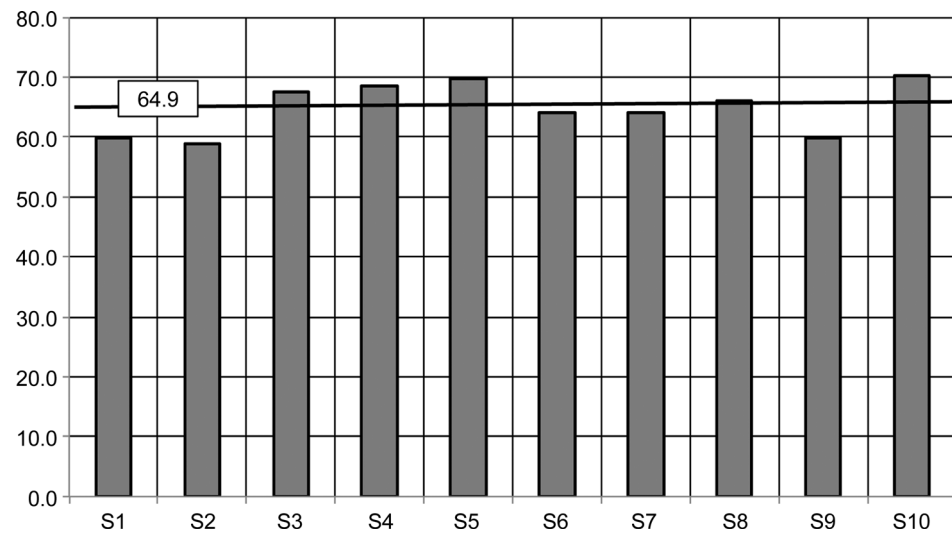
The statement with the highest percentage of high score (>3) was statement 10 on the expected effectiveness of AIs. We must consider, however, that when the survey was conducted, only the results of the MAP3 trial were available, with a remarkable 65% reduction of invasive breast cancer by exemestane (16). Subsequently, a larger trial on anastrozole, IBIS-II, showed a 50% reduction in postmenopausal women at high risk (17). Another possible influence was the fact that the results from adjuvant trials showed that AIs produced lower recurrence rates compared with tamoxifen, as emerged in a meta-analysis conducted by Dowsett and colleagues (18), suggesting that these data could be extrapolated in the prevention setting. Although AIs are probably more effective than SERMs in reducing breast cancer incidence, concerns about their tolerability and their indication only in postmenopausal women have so far limited their uptake. So the statement on AIs remains an open issue.

The second top statement was number 5 on the unavailability of ready risk models in clinical practice. The Gail model and the Tyrer-Cuzick model have been validated in prospective studies and are available on the internet (www.cancer.gov/bcrisktool/; www.ems-trials.org/riskevaluator/), but it may be cumbersome to integrate these models in the daily clinical practice, especially for primary care physicians. In a survey submitted to Californian physicians in primary care specialties, one of the leading frequent barriers to breast cancer prevention counseling was "insufficiently informed about risk reduction options" (19). In a recent UK national survey (10), only half of the GPs knew tamoxifen can reduce breast cancer risk, and only one quarter were aware of the NICE guidelines on the use of SERMs for therapeutic prevention (5). Responders asked to initiate prescribing were less willing to prescribe tamoxifen than those continuing a prescription initiated in secondary care (68.9% vs. 84.6%, $P < 0.001$). It will therefore be necessary to provide training to primary care physicians to avoid that these risk models remain accessible only to niche specialists and to ensure that they take root in primary care as it occurs for the cardiovascular risk tables to prescribe statins.

The third most commonly endorsed statement is the lack of clarity on who is the most appropriate physician for prevention advice (68.4%). Medical oncologists include among their barriers to prevention the limited time to see people without

Figure 1.

Distribution of the percentages of highly important scores (>3) for each proposed statement. S1, no mortality effect; S2, drugs have adverse events; S3, lack of reliable biomarkers; S4, unclear who is the appropriate physician; S5, risk models are difficult; S6, lack of medical knowledge; S7, prevention of curable cancers; S8, drugs have poor commercial interest; S9, Off label in EU; S10, Als better than SERMs.



cancer and some argue that prevention and control is a primary care responsibility (20). On the other side, even the percentage of women approached for therapeutic prevention in primary care practice is very low (21). Attempts to solve this barrier have apparently been successful in high-risk clinics where screening mammography is coupled with a counseling activity held by trained nurses and physicians dedicated to prevention (22).

The two statements that the authors of the questionnaire had considered most important, namely number 3 and 8 on the lack of reliable short-term biomarkers of effectiveness and the lack of commercial interest in therapeutic prevention, ranked fourth (67.5%) and fifth (66.0%), respectively. The lack of reliable short-term biomarkers is an obvious barrier considering that preventive medicine in the cardiovascular field is widely accepted and routinely used thanks to easy measurements of efficacy biomarkers, such as low-density and high-density lipoproteins and high blood pressure (9). Commercial interest is important for different reasons. First of all, there is no investment by drug companies to inform health care providers. Drug companies instead invest up to 30% of their entire budget in marketing activities for drugs under patent (23), and these marketing activities have been shown to be associated with higher prescription (24). Also, the off-patent state of these

drugs is the main cause of the absence of labeling indication at least in Europe given the lack of a clear pathway for approval for off-patent drugs (25).

The lack of mortality data is another statement with a relatively low score despite a strong scientific debate (26–28). Although studies on the mortality of women who participated in chemoprevention trials are under way, we consider prevention of breast cancer incidence still an important accomplishment because it spares the substantial adjuvant treatment morbidity, the reduced emotional and social functioning, and the deep impact on her family (29).

We wanted to compare the difference in responses between medical oncologists and the other specialists given the uncertainty on the most appropriate specialty for preventive advice. Medical oncologists have given, on average, more importance to all statements compared with nonmedical oncologists, possibly because of a greater confidence with the topic, with special reference to the lack of short-term biomarkers (OR = 2.4) and the fear of serious adverse events (OR = 1.84). The lack of short-term biomarkers, as stated before, is one of the most important barriers to breast cancer prevention in the opinion of the authors. Oncologists probably have a greater knowledge of the complexity and heterogeneous nature of cancer and the difficulty to have an early indicator of preventive efficacy such as a decrease of blood pressure or cholesterol levels in cardiovascular disease. Demonstrating, through the variation of specific early biomarkers, that the drug is effective and therefore has prevented or reduced the risk of breast cancer would certainly encourage the uptake of the drug. Fear of side effects has been reported as the main reason among women for refusing breast cancer chemoprevention (30, 31). As physician's recommendation has a key role in influencing women's decision (11), physicians should counsel women not to overestimate risks and underestimate the benefits of therapeutic prevention. The only statement to which oncologists gave less importance than other specialists is statement number 1 on the lack of mortality data. This issue is one of the main arguments against the use of antiestrogen drugs (26–28); the fact that in this survey it has a relatively low score may be due to the opinion of oncologists. Oncologists might know better that there is a lack of power in most of the preventive trials at current length of follow-up to

Table 4. Relationship between medical specialty (medical oncology vs. others) and percentage of highly important response scores (>3) estimated for each statement through logistic regression analyses

Statement	OR	95% CL
S1. No mortality effect.	0.89	0.40–1.94
S5. Risk models are difficult	1.00	0.43–2.27
S8. Drugs have no commercial interest	1.42	0.58–3.43
S10. Als better than SERMs	1.49	0.60–3.68
S4. Unclear who is the appropriate physician	1.56	0.69–3.49
S9. Off label in EU	1.57	0.68–3.62
S6. Lack of medical knowledge	1.72	0.72–4.12
S7. Prevention of curable cancers	1.74	0.73–4.12
S2. Drugs have adverse events	1.84	0.79–4.24
S3. Lack of reliable biomarkers	2.42	0.93–6.25

OR, odds ratio adjusted for gender, age at survey, and life expectancy at birth; 95% CL, confidence interval.

analyze cancer-specific and overall mortality (27) and that reducing breast cancer has itself a strong positive impact on quality of life and on health care systems, in line with the authors' opinion. Also, screening with mammography, which is the most widely used method for the control of breast cancer, has demonstrated only a modest effect on breast cancer mortality in randomized trials (32, 33).

This survey has several limitations. We collected a questionnaire to a predominance of medical oncologists and European physicians. Specifically, among the Europeans, a large slice was represented by physicians who worked in Italy (60% of the Europeans), so some of the responses may be specific to the Italian practice setting and difficult to generalize to other health systems, particularly the United States. Also, oncologists were predominantly women and worked in a country with high LEAB, which could have driven the overall response to higher scores, given that women physicians were reported to be more proactive than men in primary care for women (34) and that physicians working in a country with high LEAB are assumed to have a better knowledge of breast cancer therapeutic prevention, a relatively new field of medical oncology, also because of the highest frequency of breast cancer (1). The data were cross-sectional, prohibiting causal influence. The outcomes were self-reported, and we did not collect objective data on prescribing behavior. Finally, by using a 5-point scale, we enabled responders to fill the middle response, thus minimizing the extreme options, a phenomenon possibly associated with limited knowledge about the topic (35).

In conclusion, this survey showed a high homogeneity in giving an average importance to several reasons for the low uptake of therapeutic prevention with SERMs. However, medical oncologists gave a higher importance to the lack of surrogate biomarkers compared with other physicians. This survey provides the basis for

a better understanding of why therapeutic prevention is so under-used despite strong evidence for efficacy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acknowledgments

This work was supported by the European School of Oncology, Milan and the E.O. Ospedali Galliera, Genova. S. Noonan was the recipient of a Fondazione Umberto Veronesi fellowship.

Grant Support

S.G. Smith is funded by a Cancer Research UK Postdoctoral Fellowship (C42785/A17965).

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Received May 24, 2017; revised August 3, 2017; accepted October 12, 2017; published OnlineFirst October 23, 2017.

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