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A survey among breast cancer specialists on the low uptake of therapeutic prevention with tamoxifen or raloxifene

S. Noonan[1], A. Pasa[1], V. Fontana[2], S. Caviglia[1], B. Bonanni[3], A. Costa[4], S. G. Smith[5], F. Peccatori[6,4] and A. DeCensi[1,7]

[1] Medical Oncology, E.O. Ospedali Galliera, Genoa, Italy;

[2] Clinical Epidemiology Unit, IRCCS AOU San Martino IST, Genoa, Italy

[3] Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy.

[4] European School of Oncology Milan, Italy;

[5] Leeds Institute of Health Sciences, University of Leeds, UK

[6] Gynecologic Oncology Division, European Institute of Oncology, Milan, Italy

[7] Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK

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Corresponding author: Andrea DeCensi, MD, Division of Medical Oncology, E.O. Ospedali Galliera, Mura delle Cappuccine 14, Genoa, 16128, Italy; tel.: +39-0105634501; e-mail: andrea.decensi@galliera.it

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ABSTRACT:

BACKGROUND: To address the reasons why physicians are reluctant to prescribe breast cancer preventive therapy with the selective oestrogens receptor modulators (SERMs) tamoxifen or raloxifene despite a strong evidence of efficacy.

MATERIALS AND METHODS: 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 pre-defined 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.

RESULTS: 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).

CONCLUSIONS: 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.

INTRODUCTION

Breast cancer is the most common female tumour globally and the primary cause of cancer 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 oestrogen (ER)-positive breast cancer incidence by approximately 40% (2), with evidence for a 20 year carry-over effect in one trial (3). Currently, two SERMs are FDA approved drugs for primary breast cancer prevention: 1) tamoxifen for premenopausal and postmenopausal women at high risk of breast cancer, and 2) 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 U.S., only 0.03% aged 35 to 79 take tamoxifen and 0.2% aged 50-79 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 US (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.

DESIGN 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 last 3 years.

The questionnaire items were developed by three experts in breast cancer prevention (Bonanni B, Costa A and DeCensi A) 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 five-point Likert scale of importance. Response scores ranged from 5 to 1 as it follows: "Very important", "Important", "Moderately important", "Of little importance", "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 socio-economic 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 chi-squared test for independence. For each statement (S), response scores were described using mean and standard deviation (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 modelling (LR) was applied to scores dichotomized according to a cutoff value of 3: unimportant or moderately important (≤ 3) versus highly important (> 3) responses. LR modelling results were expressed in terms of odds ratio (OR) and corresponding 95% confidence limits (95% CL). Statistical significance of each variable in each LR model was assessed using the likelihood ratio test. In all analyses, a p-value <0.05 was considered as statistically significant. Data were analysed using Stata statistical package version 14 (StataCorp, College Station, TX. USA, 2015).

RESULTS

A total of 246 surveys were collected at different locations: 15 in Switzerland (Geneva, Oct 31, 2012), 104 in Italy (Savona, Oct 13, 2012; Meldola, Apr, 16, 2013; Genoa, Jan 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 USA, 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-value = 0.917), whereas

medical oncologists were more frequent in women (p-value = 0.002) and countries with longer LEAB (p-value < 0.001).

Table 3 summarises the scores obtained by each statement in terms of mean and standard deviations. 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 (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.

Finally, Table 4 displays the results of ten 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). Secondly, 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). Since 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.

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 et al. (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% versus 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 nich 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 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, 27, 28). While studies on the mortality of women who participated in chemoprevention trials are underway, 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 to non-medical 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). Since physician's recommendation has a key role in influencing women 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 anti-estrogen drugs (26, 27, 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 analyze cancer specific and overall mortality (27) and that reducing breast cancer has itself a strong

positive impact on quality of life and on healthcare 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 behaviour. 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 underused despite strong evidence for efficacy.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86.
2. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 2013;381(9880):1827-34.
3. Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol 2015;16(1):67-75.
4. Visvanathan K, Hurley P, Bantug E, Brown P, Col NF, Cuzick J et al. Use of pharmacologic interventions for breast cancer risk reduction: American society of clinical oncology clinical practice guideline. J ClinOncol 2013;31(23):2942–2962.
5. National institute for health and clinical excellence. Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. CG164:2013.
6. National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology: Breast cancer risk reduction, v. 2.2009. http://www.nccn.org.
7. Smith SG, Sestak I, Forster A, Partridge A, Side L, Wolf MS et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. Annals of Oncology 2016;27(4):575-590.
8. Waters EA, McNeel TS, Stevens WM, Frredman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat. 2012;134(2):875–880.
9. DeCensi A, Thorat MA, Bonanni B, Smith SG, Cuzick J. Barriers to preventive therapy for breast and other major cancers and strategies to improve uptake. Ecancer medical science 2015;9:595.
10. Smith SG, Foy R, McGowan JA, Kobayashi LC, DeCensi A, Brown K, et al. Prescribing tamoxifen in primary care for the prevention of breast cancer: a national online survey of GPs' attitudes. Br J Gen Pract 2017. Feb 13 [Epub ahead of print] PubMed PMID: 28193617.
11. Kinney AY, Richards C, Vernon SW, Vogel VG. The effect of physician recommendation on enrollment in the breast cancer chemoprevention trial. PrevMed 1998;27(5 Pt 1):713–719.
12. Boynton PM, Greenhalgh T. Selecting, designing, and developing your questionnaire. BMJ 2004;328(7451):1312-5.
13. Richardson J. Design and conduct a survey. Complement Ther Med. 2005; 13(1):47-53.
14. Likert R. Technique for the measure of attitudes. Arch. Psycho. 1932; 22(140):1-55.
15. WHO. World health statistics 2015. Part II. http://www.who.int/gho/publications/world_health_statistics/2015/en/, last access 21/11/2016.

16. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 2011;364(25): 2381-91.
17. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 2014;383(9922):1041-8.
18. Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol. 2010; 20;28(3):509-18.
19. Kaplan CP, Haas JS, Pérez-Stable EJ, Des Jarlais G, Gregorich SE. Factors affecting breast cancer risk reduction practices among California physicians. Prev Med. 2005;41(1):7-15.
20. American Society of Clinical Oncology, Ganz PA, Kwan L, Somerfield MR, Alberts D, Garber JE, et al. The role of prevention in oncology practice: results from a 2004 survey of American Society of Clinical Oncology members. J Clin Oncol. 2006;24:2948-2957.
21. Armstrong K, Quistberg DA, Micco E, Domchek S, Guerra C. Prescription of tamoxifen for breast cancer prevention by primary care physicians. Arch InternMed 2006;166:2260-2265.
22. Evans DG, Howell A. Can the breast screening appointment be used to provide risk assessment and prevention advice? Breast Cancer Res 2015;17:84.
23. Socolar D, Sager A. Pharmaceutical marketing and research spending: The evidence does not support PhRMA's claims. 2001. www.bu.edu.
24. Engelberg J, and Parsons CA, Tefft N. Financial Conflicts of Interest in Medicine. 2014. Available at SSRN: https://ssrn.com/abstract=2297094.
25. Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst 2007;99(4):258–260.
26. Narod SA. Tamoxifen Chemoprevention--End of the Road? JAMA Oncol 2015; 1(8): 1033-4.
27. Cuzick J, Wickerham L, Powles T. Differing Perspectives on Breast Cancer Chemoprevention. JAMA Oncol 2016;2(2):276-7.
28. Cameron DA. Breast cancer chemoprevention: little progress in practice? Lancet 2014; 22;383(9922):1018-20.
29. Gavric Z. Quality of Life of Women with Breast Cancer-Emotional and Social Aspects. Am J Cancer Prev 2015;3(1):13-18.
30. Port ER, Montgomery LL, Heerdt AS, Borgen PI. Patient reluctance toward tamoxifen use for breast cancer primary prevention Ann Surg Oncol 2001;8(7)580–585.
31. Bober SL, Hoke LA, Duda RB, Regan MM, Tung NM. Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. J Clin Oncol 2004;22(24):4951–4957.
32. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S et al. Benefits and Harms of Breast Cancer Screening: A Systematic Review. JAMA 2015;314(15):1615-34.
33. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet 2012;380(9855):1778-86.

34. Lurie N, Slater J, McGovern P, Ekstrum J, Quam L, Margolis K. Preventive care for women. Does the sex of the physician matter? N Engl J Med 1993;329(7):478-82.
35. Kalton Roberts J, Holt D. The effects of offering a middle response option with opinion questions. J R Stat Soc 1980;29:65-78.

Table 1. 10 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 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 since all approved drugs are out of patent.
S9	The use of these drugs has not been approved in Europe and its prescription outside the US 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-value
	Other medical area		Medical oncology		Unknown		
	No.	%	No.	%	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

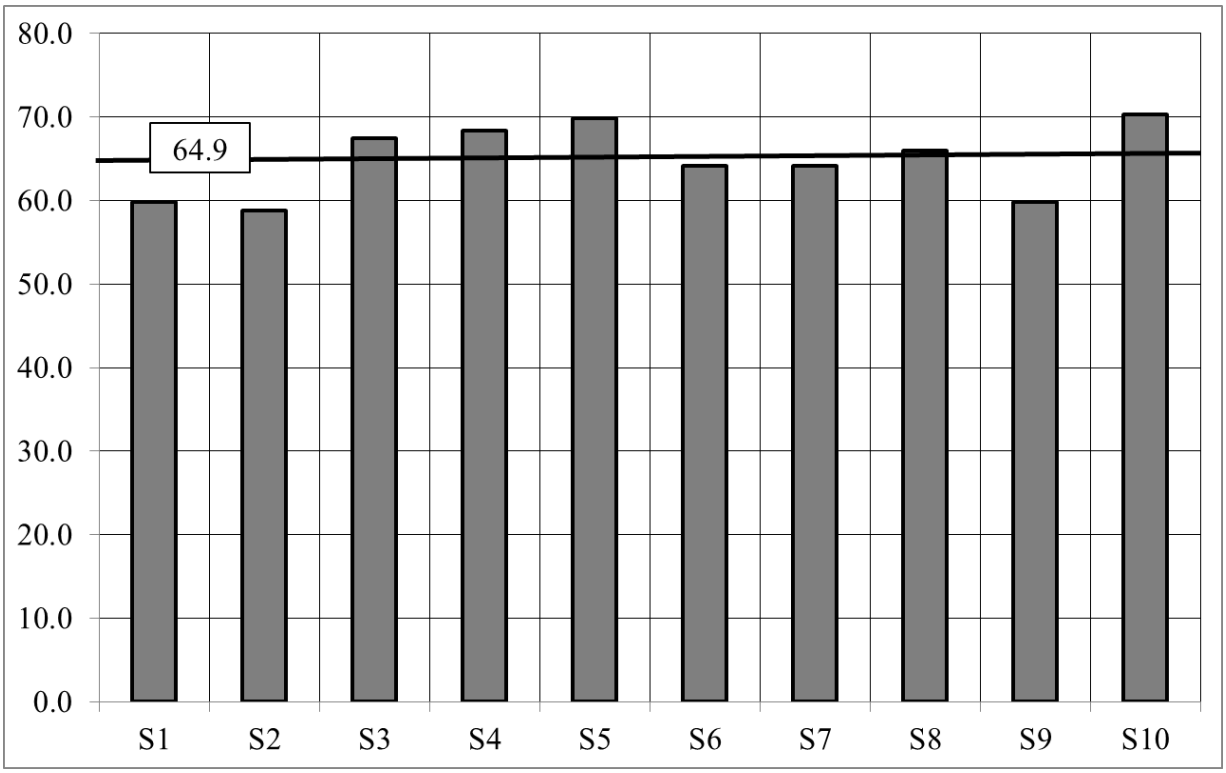
LEAB: life expectancy at birth; p-value of the chi-squared test for independence

Table 3 – Mean scores and corresponding standard deviations (SD) for each statement

Statement	Mean	SD	p-value
S1. No mortality effect	3.1	1.2	0.293
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	
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	

Score 5=very important, score 1=unimportant; p-value with the Kruskal-Wallis nonparametric rank test

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. AIs better than SERMs

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. AIs 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 limits.