Preventive treatments for breast cancer: recent developments

J. E. Alés-Martínez · A. Ruiz · J. I. Chacón · A. Lluch Hernández · M. Ramos · O. Córdoba · E. Aguirre · A. Barnadas · C. Jara · S. González · A. Plazaola · J. Florián · R. Andrés · P. Sánchez Rovira · A. Frau

Received: 20 February 2014 / Accepted: 17 October 2014 / Published online: 2 December 2014
© Federación de Sociedades Españolas de Oncología (FESEO) 2014

Abstract Breast cancer is a burden for western societies, and an increasing one in emerging economies, because of its high incidence and enormous psychological, social, sanitary and economic costs. However, breast cancer is a preventable disease in a significant proportion. Recent developments in the armamentarium of effective drugs for breast cancer prevention (namely exemestane and anastrozole), the new recommendation from the National Institute for Health and Care Excellence to use preventative drugs in women at high risk as well as updated Guidelines from the US Preventive Services Task Force and the American Society of Clinical Oncology should give renewed momentum to the pharmacological prevention of breast cancer. In this article we review recent major developments in the field and examine their ongoing repercussion for breast cancer prevention. As a practical example, the potential impact of preventive measures in Spain is evaluated and a course of practical actions is delineated.

Keywords Breast cancer · Pharmacological prevention · GEICAM · Aromatase inhibitors · BRCA · Breast cancer prevention

This study is conducted on behalf of GEICAM

J. E. Alés-Martínez (✉)
Hospital Nuestra Señora de Sonsoles, GEICAM Spanish Breast Cancer Group, Ávila, Spain
e-mail: jealesm@seom.org

A. Ruiz
Instituto Valenciano de Oncología (IVO), GEICAM Spanish Breast Cancer Group, Valencia, Spain

J. I. Chacón
Hospital Virgen de la Salud, GEICAM Spanish Breast Cancer Group, Toledo, Spain

A. Lluch Hernández
Hospital Clínico Universitario de Valencia/INCLIVA, Universidad de Valencia, GEICAM Spanish Breast Cancer Group, Valencia, Spain

M. Ramos
Centro Oncológico de Galicia, GEICAM Spanish Breast Cancer Group, A Coruña, Spain

O. Córdoba
Hospital Universitari Vall d’Hebron, GEICAM Spanish Breast Cancer Group, Barcelona, Spain

E. Aguirre
Hospital Universitari Arnau de Vilanova, GEICAM Spanish Breast Cancer Group, Lleida, Spain

A. Barnadas
Hospital de la Santa Creu i Sant Pau, GEICAM Spanish Breast Cancer Group, Barcelona, Spain

C. Jara
Hospital Universitario Fundación Alcorcón, GEICAM Spanish Breast Cancer Group, Madrid, Spain

S. González
Hospital San Pedro de Alcántara, GEICAM Spanish Breast Cancer Group, Cáceres, Spain

A. Plazaola
Onkologikoa, GEICAM Spanish Breast Cancer Group, Guipúzcoa, Spain

J. Florián
Hospital de Barbastro, GEICAM Spanish Breast Cancer Group, Huesca, Spain
Introduction

In spite of its demonstrated efficacy, the pharmacological prevention of breast cancer is still struggling to make a substantial impact in terms of population uptake and public health repercussions due to a variety of reasons, related in part to perceived risks of severe side effects caused by tamoxifen but also because of lack of a unequivocal impulse and support on the part of health authorities and breast cancer professionals and organisations. Recent scientific, institutional and public awareness developments could perhaps provide the necessary momentum to change this scenario. From the scientific point of view there have been two significant additions to the armamentarium of effective drugs to prevent breast cancer in postmenopausal women, namely exemestane and anastrozole. At the same time, there has been a wealth of social and media repercussions related to known celebrities. Institutions like National Institute for Health and Care Excellence (NICE) have included the recommendation for chemoprevention for certain populations and the US Preventive Services Task Force (USPSTF) and the American Society of Clinical Oncology (ASCO) have provided updates of their stance on Breast Cancer Prevention. Please note that we are endorsing the use of preventive treatment instead of chemotherapy, not only in Spain but in most other countries as well [1].

BRCA associated breast cancer: the Jolie effect

In chronological order, the first news to hit the headlines with very broad circulation was the coverage of the announcement of Angelina Jolie’s decision in May 2013 to undergo prophylactic bilateral mastectomy [2] because she was a carrier of a deleterious mutation in BRCA1. Although this is a common practice among women carriers of this condition, the way in which the news was communicated led some people to believe that this was a measure that was applicable to a much wider population. There is certainly the need for greater collaboration between the media and the experts in order to improve how news of this kind is presented, and also a more thorough explanation of the context is required by the doctors. It is also extremely important to have programmes of continuing training for general practitioners and other specialists, who are the ones to first receive requests for information from women patients. Generally speaking, the Jolie effect has been positive worldwide and used by doctors and professional societies alike to reinforce messages of prevention in this high risk population. A recent work by J. Raphael et al. [3] has shown a doubling in the use of BRCA testing in the 6 months after Jolie’s announcement. Importantly this increase was correctly requested since the positivity rate remained constant. Nonetheless, even when appropriate this rise in genetic counselling and testing conveys increased costs for Health Systems that should be accounted for. For women carriers of a BRCA mutation, prophylactic mastectomies can save lives not only when performed before a cancer diagnosis but also after having being diagnosed of a first breast tumour, as shown in new studies [4]. That is also the case for prophylactic salpingooophorectomies [5]. However, as a modelling work recently found out, contralateral mastectomy will probably not provide significant benefits in breast cancer women with average risk [6]. The key message we should give to our patients, relatives and to carriers or individuals with a high risk of deleterious mutations in these genes, is that knowledge of their genetic state can lead to the application of measures that can save lives, both of subjects who have not already had any of the associated diseases, and of individuals who have already had the early stages of one of the primary tumour. In parallel, it is important to remember to convey the important message that women carriers of the BRCA mutations, who develop cancer, do not have a worse prognosis of their disease than sporadic breast cancer [7]. Although, in the metastatic disease a cure still seems to be out of our grasp, the new generation of clinical trials with better-targeted treatments could create new standards with better survivals and management of this group of diseases, both of those linked and those not linked to BRCA.

NICE discovers chemoprevention

The second piece of news that also had an important media impact, and its fair share of misinterpretations, was the recommendation by the British National Institute for Health and Care Excellence, better known as NICE, for tamoxifen and raloxifene to be considered as agents with positive cost-effectiveness, the use of which should be encouraged in the National Health Service. In some cases, the media combined this news with the previous one, hastily concluding that tamoxifen was a new medication...
that could prevent the need for mastectomies in women carriers of the BRCA mutation. This confusion could have partly arisen from the fact that tamoxifen and raloxifene were referred to in the GC164 guidelines “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” published on 25th June 2013 [8]. The reference to oestrogen receptor antagonists is included in point 1.7 “Risk reduction and treatment strategies”. Although a family history is not a mandatory criterion, the guideline does call for the estimated risk to develop cancer from 20 years onwards to be “moderate” (between 18 and 19 % in their lifetime or from 3 to 8 % in their forties) or “high” (more than 30 % total lifetime risk or higher than 8 % in their forties) (Table 1, adapted from reference [8]).

In fact, the general recommendation is to offer tamoxifen (premenopausal women), or tamoxifen or raloxifene to postmenopausal women with a high risk (see definition in Table 1) for 5 years, unless they have a family history of thromboembolic disease or cancer of the uterus. This recommendation would, therefore, only hold for the group with the least solid evidence available for prevention. It is important to emphasize that seminal prevention studies with tamoxifen or raloxifene [9–11] have not specifically targeted high risk populations, but instead moderate risk ones, being equivalent, in American trials, to the baseline risk of breast cancer in a 60-year-old woman without any other risk factors, corresponding to an approximate risk of developing breast cancer in 5 years of 1.7 % [12]. In British studies, algorithms have been used that assign more relevance to family history [13, 14]. In any case, both levels of risk are well below those suggested in the NICE guidelines. Intuitively, one could say that the higher the baseline risk of a population, the more likely that an intervention will be successful, with a favourable cost-effectiveness ratio. In the case of tumours linked to BRCA, tamoxifen seems to reduce the incidence of primary or contralateral tumour, similarly to non-genetically predisposed patients. However, the data available have been obtained retrospectively with a low number of patients in randomised trials, or correspond to non-prospective cohort studies [15–18]. On the other hand limiting the use of tamoxifen or other agents to these very high risk populations would limit their true preventive potential and the possibility of obtaining benefits on a larger scale. If we draw a parallel with the use of lipid-lowering drugs, if we only used these medications in carriers of severe hereditary hypercholesterolemia, we would be stripping them of their broad preventive cardiovascular effectiveness in the general population.

An interesting practical point is that the NICE recommendation has been made in spite of the fact that neither tamoxifen nor raloxifene are authorised for this indication in the UK or in any other country of the European Union. This is why the guidelines say that “the prescriber should follow relevant professional recommendations, accepting full responsibility for his/her decision. The patient must provide informed consent that must be documented”. This context can be equated to the Spanish situation, and in our opinion could be considered as a procedural reference. Informed consent records are a key aspect that should be systematically incorporated when using agents for indications that do not have the approval of the AEMPS or the EMA.

It is worth mentioning that NICE update was preceded by the direct recommendation by a group of experts in the St. Gallen conference of 2010 that NICE and other governmental and regulatory bodies use specific and differentiated criteria to evaluate preventive treatments [1]. The corollary is that the Spanish Society of Medical Oncology (SEOM) and Breast Cancer Oriented Cooperative Groups like the GEICAM Spanish Breast Cancer Group and others should make their voice heard by the corresponding authorities in the same way.

ASCO (mainly) and the US Preventive Services Task Force (USPSTF) reinforce their message about prevention in breast cancer

In April 2013, the USPSTF updated the recommendations they had developed back in 2002 (11 years earlier) [19]. They acknowledge that they have taken mainly into consideration the update of the STAR study data, which showed that with an 81-month follow-up, the preventive effectiveness of tamoxifen was greater than that of raloxifene [20]. Unlike the NICE guidelines, these are more general recommendations, only reinforcing the message for the highest risk women, and make the assumption that women with a history of atypical dysplasia or lobular carcinoma in situ could benefit the most, based on data of the NSABP P1 trial and another observational study

### Table 1 Breast cancer risk classification

| Risk similar to the population | Moderate risk | High risk |
|--------------------------------|--------------|----------|
| Lifetime risk after 20 years old | 17% or less | More than 17% but less than 30% | 30% or more |
| Risk between 40 and 50 years old | 3–8% | More than 8% |

*This group includes known mutations in the BRCA1, BRCA2 and TP53 genes and other rarer diseases with a high risk of breast cancer such as Peutz–Jegher syndrome (STK11), Cowden (PTEN) and hereditary diffuse gastric cancer (E-cadherin)*
Table 2  Comparison of recommendations by agencies

| Agent | ASCO (ref. [25]) | USPTF (ref. [19]) | NICE (ref. [8]) |
|-------|------------------|-------------------|----------------|
| Tamoxifen | Premenopausal women ≥35 years old with a 5-year projected absolute BC risk ≥1.66 % or with LCIS | Premenopausal women aged ≥35 years who are at increased risk for breast cancer without a prior diagnosis of breast cancer, DCIS or LCIS | Offer to premenopausal women at high risk of breast cancer |
|       | Postmenopausal women ≥35 years with a 5-year projected absolute BC risk ≥1.66 % or with LCIS | Postmenopausal women aged ≥35 years who are at increased risk for breast cancer without a prior diagnosis of breast cancer, DCIS or LCIS | Consider for premenopausal women at moderate risk of breast cancer |
|       | Not recommended if history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilisation | Not to be used in women with a history of thromboembolic events (deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack) | Offer to postmenopausal women with or without a uterus and at high risk of breast cancer |
|       | Not recommended in combination with hormone therapy | Not recommended if they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer or bilateral mastectomy | Consider for postmenopausal women with or without a uterus and at moderate risk of breast cancer |
|       | Not recommended for pregnant women, women who may become pregnant, or nursing mothers | | |
| Raloxifene | Postmenopausal women who are ≥35 years old with a 5-year projected absolute BC risk ≥1.66 % or with LCIS | Postmenopausal women aged ≥35 years who are at increased risk for breast cancer without a prior diagnosis of breast cancer, DCIS or LCIS | Offer to postmenopausal women with a uterus and at high risk of breast cancer |
|       | Should not be used for BC risk reduction in premenopausal women | Not recommended if they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer or bilateral mastectomy | Consider for postmenopausal women with a uterus and at moderate risk of breast cancer |
|       | Not recommended if history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack or during prolonged immobilisation | | |
| Exemestane | Alternative in postmenopausal women ≥35 years old with a 5-year projected absolute BC risk ≥1.66 % or with LCIS or atypical hyperplasia | Not included | Not included |
|       | Should not be used for BC risk reduction in premenopausal women | | |
| Anastrozole | Not included | Not included | Not included |
| ALL | Risks and benefits of each agent in the preventive setting specifically should be discussed prior to prescription | Engage in shared, informed decision | |
| Minimum breast cancer risk required | For tamoxifen and raloxifene, a 5-year projected absolute BC risk ≥1.66 % or with LCIS | Estimated 5-year breast cancer risk of 3 % or greater | High risk: lifetime risk of 30 % or greater; risk of >8 % in between age 40 and 50 years |
|       | For exemestane, a 5-year projected absolute BC risk ≥1.66 % or LCIS or atypical hyperplasia | | Moderate risk: lifetime risk of 17 % but <30 %; a risk of 3–8 % between age 40 and 50 years |
comprising more than 2,500 women [9, 21]. Another noteworthy part of this report is the exhaustive analysis of 13 risk stratification methods. On the whole, all of them seem to offer similar results. In other words, they are effective at the population level, with predictive capacities over 90 %, but perform poorly in relation to concordance, or the ability to determine individual risk (they barely obtain areas under the curve higher than 0.6). Two recent Spanish studies have produced similar results, also confirming the importance of mammographic density as a decisive risk factor [22, 23]. It is interesting that although the results of the MAP.3 study [24] are cited, exemestane is not expressly included among the agents to be considered (this also occurs with the NICE guidelines), perhaps because of not being approved yet for the preventive indication in the US.

With even greater diffusion, ASCO has also updated its guidelines, for which the previous version was published in 2009. In this new edition [25], the term “chemoprevention” has been replaced by the term “pharmacological interventions to reduce the risk of breast cancer”. A literature review of studies published between 2007 and 2012 included a review not only of tamoxifen and raloxifene but also of arzoxifene, lasofoxifene, exemestane and anastrozole. In accordance with the available evidence, their recommendations are much broader. Specifically, tamoxifen is recommended in premenopausal women and tamoxifen, raloxifene or exemestane in postmenopausal women, provided that they comply with inclusion criteria established in the clinical trials for these agents (a five-year risk higher than 1.67 %, lobulillar hyperplasia) and always personalising the advice, tailoring it to the risks and benefits of each case. As a general rule, the preventive benefit tends to be greater as the estimated risk increases. In this line, the study by Freedman et al., [26] is very useful. It stratifies the risks and benefits relative to patients’ age, and is also adapted to take into account the STAR update [20], which shows the greater long-term preventive capacity of tamoxifen, and the very positive data of the Excel study [24], showing a 65 % reduction in breast cancer incidence compared to placebo. As we mentioned before, a truly preventive strategy must be applicable to a large population. Only in this way can the huge social, family, personal and financial impact of breast cancer in western societies be reduced.

The intention of ASCO with this update is, essentially, to emphasize the enormous potential for health of preventive intervention in breast cancer, strengthening the tone of the indications, which changes from one that makes suggestions in the previous edition, to making strong recommendations in the current version, with an explicit order to doctors to discuss these options with their potential beneficiaries. This would perhaps manage to raise the number of people who choose prevention, something which has not occurred over the past 10 years [27] by a variety of reasons, including lack of awareness and fear of side effects.

Table 2 summarizes the main features of NICE, USPTF and ASCO recommendations and Table 3 shows the characteristics of the Gail 2 and Tyrer–Cuzick risk prediction models.

**The application of therapeutic prevention of breast cancer in Spain**

There are great opportunities in Spain to apply breast cancer prevention and improve public health by pharmacological intervention. There are approximately 25,000 new cases of breast cancer each year in our country, and over 6,000 deaths from this cause [28]. Of these cases, approximately 14,000 occur in women over 55 years old. It is clear that, if prevention is feasible, a large number of high impact medical interventions could be avoided (surgical interventions, chemotherapies, radiotherapy) and also the psychological, social and work-related costs and the long-term consequences of treatments in survivors of the disease. In the rationale given by NICE for the recommendation for the pharmacological prevention of breast cancer, it was estimated that each case of breast cancer prevented would cost far less than the willingness-to-pay threshold of £20,000 per QUALY of the English NHS, even given the conservative level of effectiveness taken of 35 %, considered to be the same for tamoxifen and

### Table 3 Methods more frequently used to identify women at increased risk for breast cancer

| Method | Main features | Used in |
|--------|---------------|---------|
| The Gail 2 model or Breast Cancer Risk Assessment Tool (ref. [12]; can be accessed at [www.cancer.gov/bcrisktool](http://www.cancer.gov/bcrisktool)) | It estimates the absolute risk of developing breast cancer in the next 5 years based on: age, age at menarche, age of first birth, family history of breast cancer in first degree relatives, number of previous breast biopsies, and history of atypical hyperplasia | NSABP-I [9] STAR [11] MAP.3 [24] |
| The Tyrer-Cuzick model (ref. [13]; can be downloaded at [http://www.ems-trials.org/riskevaluator/](http://www.ems-trials.org/riskevaluator/)) | It estimates the risk taking into account family history, hormonal and benign disease history, age, BMI and genetic factors (including BRCA) creating a single statistical model | IBIS-II [30] |
raloxifene. In Spain, we know that efficacy data in the Spanish cohort included by GEICAM in the MAP.3 study are comparable to those of its whole population, in spite of there being some differences in relation to baseline level of estimated risk and mean age of the participants [29]. By extrapolating the 65 % reduction in risk obtained in the study to data for the Spanish population we can estimate that between 7,000 and 9,000 cases of breast cancer could be prevented in postmenopausal women per year. These figures could be improved with the correct use of tamoxifen in premenopausal women. From these data, firstly we can infer the very great responsibility that doctors have to convey this information to those responsible for health policies and financing and, secondly, the urgent need to conduct pharmaco-economic studies to validate and support, also from an economic perspective, the value of pharmacological prevention of breast cancer.

**Preventive effect and tolerability of aromatase inhibitors are confirmed**

As mentioned before, the MAP.3 trial showed a 65 % reduction in the incidence of invasive breast cancer in women treated with exemestane as compared to placebo [24]. More recently, Cuzick et al. [30] revealed the IBIS II trial results. This study compared anastrozole and placebo in a population of over 3,900 women with higher risk of developing breast cancer. After a 5-year follow-up the authors demonstrated a 50 % reduction in the incidence of overall and invasive breast cancer in women taking anastrozole. This is somewhat less than the reduction observed in MAP.3 but differences in populations and follow-up could account for this variance. A meta-analysis of these two big trials will help define if there is some incremental benefit in any subgroup. However, anastrozole also showed a greater preventive efficacy than tamoxifen, which lead Dr. Cuzick to the conclusion that aromatase inhibitors are the primary prevention treatment of choice in postmenopausal women. As in MAP.3 and other intervention trials, prevention was seemingly restricted to receptor positive breast cancer. Preventive drugs must have an outstanding tolerability, in addition to efficacy and safety, if they are to be accepted by a healthy population. The results of the Quality of Life substudy from MAP.3 study have been published recently [31]. Exemestane had small negative effects on vasomotor symptoms, sexual life and pain, but only in 4 % more women than in the placebo arm. Overall, the apparently limited impact on quality of life makes exemestane a suitable agent for pharmacological prevention. The placebo controlled nature of the study gives more strength to the results.

**Summary and take home messages**

Pharmacologic prevention of breast cancer is a solid reality supported by numerous well designed trials. Uptake by the general population has been difficult due in part to the risks, real and perceived, attributed to preventive drugs, especially tamoxifen. Also there has not been a massive commitment of Public Health authorities and professional societies as the one undertaken in the past to spread the use of blood pressure and cholesterol reducing agents. Based on MAP.3 and IBIS II results, exemestane and anastrozole could probably become the new standard for postmenopausal women seeking a reduction in their breast cancer risk. Tamoxifen remains the sole proven drug in premenopausal women. Investigation must continue to provide new drugs with better tolerability and ability to prevent hormone receptor negative breast cancer. Efforts must be made to further characterise the health and economics benefits of preventing breast cancer.

**Conflict of interest** None.

**References**

1. Cuzick J, DeCensi A, Arun B, Brown PH, Castiglione M, Dunn B, et al. Preventive therapy for breast cancer: a consensus statement. Lancet Oncol. 2011;12(5):496–503.
2. Jolie A. My medical Choice. Published on May 14, 2013 in the NY Times. http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?emc=eta1&_r=3. Last Accessed 12 Oct 2014.
3. Raphael J, Verma S, Hewitt P, Eisen A. The impact of Angelina Jolie’s (AJ) story on genetic referral and testing at an academic cancer centre. J Clin Oncol. 2014;32. (suppl 26; abstr 44).
4. Metcalfe K, Gershman S, Ghadirian P, Lynch HT, Snyder C, Tung N, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. BMJ. 2014;11(348):g226. doi:10.1136/bmj.g226.
5. Portisch PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic mastectomy: a decision analysis. JNCI J Natl Cancer Inst. 2014;106(8):dju160. doi:10.1093/jnci/dju160.
6. Obermair A, Youlden DR, Baade PD, Janda M. The impact of risk-reducing hysterectomy and bilateral salpingo-oophorectomy on survival in patients with a history of breast cancer—a population-based data linkage study. Int J Cancer. 2014;134(9):2211–22. doi: 10.1002/ijc.28537. Epub 2013 Oct 31.
7. Huzarski T, Byrski T, Gronwald J, Gorski B, Domagala P, Cybulski C, et al. Ten-year survival in patients with BRCA1-negative and BRCA1-positive breast cancer. J Clin Oncol. 2013;31(26):3191–6.
8. http://guidance.nice.org.uk/CG164.
9. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst. 2005;97(22):1652–62.
10. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, et al. International Breast Cancer Intervention Study I Investigators. Long term results of Tamoxifen prophylaxis for breast cancer96 month follow up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99(4):272–82.
11. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of Tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of Tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727–41 Epub 2006 Jun 5.
12. Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst. 1999;91:1541–8.
13. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23:1111–30.
14. Boughey JC, Hartmann LC, Anderson SS, Degnim AC, Vierkant RA, Reynolds CA, et al. Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol. 2010;28:3591–6.

15. Kote-Jarai Z, Powles TJ, Mitchell G, Tidy A, Ashley S, Easton D, et al. BRCA1/BRCA2 mutation status and analysis of cancer family history in participants of the Royal Marsden Hospital tamoxifen chemoprevention trial. Cancer Lett. 2007;247(2):259–65.

16. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2004;22(12):2328–35.

17. Phillips KA, Milne RL, Rookus MA, Antoniou AC, Peock S, et al. Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J Clin Oncol. 2013;31:3091–9.

18. Vicus D, Rosen B, Lubinski J, Domchek S, Kauff ND, Lynch HT, et al. Tamoxifen and the risk of ovarian cancer in BRCA1 mutation carriers. Gynecol Oncol. 2009;115(1):135–7.

19. Nelson HD, Smith ME, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the US preventive services task force. Ann Intern Med. 2013;158(8):604–14.

20. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Update of the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res (Phila). 2010;3(6):696–706. doi: 10.1158/1940-6207.CAPR-10-0076. Epub 2010 Apr 19.

21. Coopey SB, Mazzola E, Buckley JM, Shariko J, Belli AK, Kim EM, et al. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Breast Cancer Res Treat. 2012;136:627–33.

22. Pastor-Barriuso R, Ascunce N, Erdozáin N, Murillo A, Alés-Martínez JE, et al. Recalibration of the Gail model for predicting invasive breast cancer risk in Spanish women: a population-based cohort study. Breast Cancer Res Treat. 2013;136(1):249–59.

23. Pollán M, Ascunce N, Ederra M, Murillo A, Ezozán N, Alés-Martínez JE, et al. Mammographic density and risk of breast cancer according to tumor characteristics and mode of detection: a Spanish population-based case-control study. Breast Cancer Res. 2013;15(1):R9.

24. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. NCIC CTG MAP.3 Study investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381–91.

25. 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 Clin Oncol. 2013;31:2942–62.

26. Freedman AN, Yu B, Gail MH, Costantino JP, Graubard BI, Vogel VG, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. J Clin Oncol. 2011;29:2327–33.

27. Waters EA, McNeel TS, Stevens WM, Freedman AN. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat. 2012;134(2):875–80.

28. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer incidence and mortality worldwide: IARC CancerBase No. 10, Lyon, France: International Agency for Research on Cancer; 2012. http://globoiarc.fr. Accessed 13 Oct 2014.

29. Alés JE, Ruiz A, Richardson H, Chacón I, Lluch A, Ramos M, et al. Map.3/Excel/GEICAM 2003-08: an international phase III placebo-controlled breast cancer prevention trial of exemestane in postmenopausal women at risk for breast cancer: results of the Spanish cohort. XIII CONGRESO NACIONAL SEOM. Málaga, 19–21 Oct, 2011.

30. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cowthorn 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. doi: 10.1016/S0140-6736(13)62292-8.

31. Maunsell E, Goss PE, Chlebowski RT, Ingle JN, Alés-Martínez JE, Sarto GE, et al. Quality of Life in MAP.3 (Mammary Prevention 3): A Randomized, Placebo-Controlled Trial Evaluating Exemestane for Prevention of Breast Cancer. J Clin Oncol 2014;32:1427–36.