HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2017 July 13.

Published in final edited form as:

Breast Cancer Res Treat. 2016 June ; 157(2): 319–327. doi:10.1007/s10549-016-3805-0.

An international survey of surveillance schemes for unaffected *BRCA1* and *BRCA2* mutation carriers

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Conflict of Interest: All authors declare that they have no conflict of interest.

Author declaration: All Authors declare that they do not have a financial relationship with the organization that sponsored the research, as this research project was not supported or funded by any organization.

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Abstract

Purpose—Female *BRCA1/BRCA2* mutation carriers are at substantially increased risk for developing breast and/or ovarian cancer, and are offered enhanced surveillance including screening from a young age and risk-reducing surgery (RRS)-mastectomy (RRM) and/or salpingo-oophorectomy (RRSO). While there are established guidelines for early detection of breast cancer in high-risk women who have not undergone RRM, there are less developed guidelines after RRM. We evaluated the schemes offered before and after RRS in internationally diverse high-risk clinics.

Methods—An e mailed survey distributed to high-risk clinics affiliated with CIMBA.

Results—Overall, 22 centers from 16 countries responded. Pre RRS surveillance schemes overwhelmingly included breast imaging (primarily MRI) from 18–30 years and clinical breast exam (CBE) at 6–12 month intervals. For ovarian cancer, all but 6 centers offered semiannual/annual gynecological exam, transvaginal ultrasound, and CA 125 measurements. Post RRM, most centers offered only annual CBE while 4 centers offered annual MRI, primarily for substantial residual breast tissue. After RRSO only 4 centers offered specific gynecological surveillance.

Conclusions—Existing guidelines for breast/ovarian cancer detection in *BRCA* carriers are being applied pre RRS but are not globally harmonized, and most centers offer no specific surveillance post RRS. From this comprehensive multinational study it is clear that evidence-based, long term prospective data on the most effective scheme for *BRCA* carriers post RRS is urgently needed.

Keywords

BRCA1/BRCA2 mutation carriers; high-risk women; early detection; risk reducing surgery; Surveillance schemes

Introduction

Women who carry germline mutations in the *BRCA1* or *BRCA2* genes are at a substantially high risk for developing breast and ovarian/fallopian tube cancer, estimated to be up to 7 and 25 times that of the average risk population, respectively [1]. These high-risk mutation carriers are offered an intensified surveillance scheme aimed at early detection of breast cancer that includes clinical breast exam (CBE) by a physician or a trained health care professional and breast imaging (mammography and/or MRI, the latter in the young age group) starting mostly at 25–30 years of age and performed at 6–12 month intervals [2]. Due to the lack of efficient early detection scheme for ovarian/fallopian tube cancer, women are advised to undergo risk reducing salpingo-oophorectomy (RRSO) after completing

childbearing at 35–40 years of age [3], or as an interim procedure that still lacks proof of long term effectiveness, bilateral salpingectomy [4]. RRSO reportedly also reduces the risk for developing breast cancer when performed before age 35–40 years of age [5–7], though this notion has recently been challenged [8]. Use of chemoprevention measures such as selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) for breast cancer risk reduction in high-risk women who are pre-and post-menopausal, respectively [9], and oral contraceptive use for ovarian cancer risk reduction [4] may also be considered. Currently the most effective method for active breast cancer risk reduction is risk reducing mastectomy (RRM) [6, 10]. Indeed, risk reducing surgery (RRS) has been shown to be associated with a substantial decrease in breast and ovarian cancer risks in *BRCA* mutation carriers [3, 11, 12]. To streamline and centralize care of women at increased breast ovarian cancer risk, high-risk clinics have been established in many countries since the early-mid 1990's [13–15].

Although there are established guidelines for the above listed early detection schemes in women who have not undergone risk reducing surgeries [e.g., National Comprehensive Cancer Network (NCCN) [http://www.nccn.org/professionals/physician_gls/f_guidelines.asp] and National Institute for health and care excellence (NICE) [https://www.nice.org.uk/], the recommendations and practices for *BRCA* mutation carriers after RRS are less well established and less harmonized, as it is not clear whether any surveillance regimen is necessary, effective and cost-beneficial. The aim of the current study was to define the various surveillance regimens and local practices offered in different high-risk clinics in Asia, Australia, Europe, and North America, and specifically focusing on post RRM and RRSO practices.

Methods

A questionnaire was e-mailed to all representatives (n= 64) of countries or high-risk clinics affiliated with CIMBA [The Consortium of Investigators of Modifiers of BRCA1/2 - http://apps.ccge.medschl.cam.ac.uk/consortia/cimba//] in June 2015. Responses were e-mailed back and analyzed.

Results

Overall, there were 22/64 respondents (34.3%): 10 centers from European countries, 6 from the USA, 2 from Australia, and one each from Canada, Hong Kong, Korea, and Israel (Table 1). The respondents from Germany, Austria, Belgium, Korea, the Netherlands, Poland and Sweden represent the recommended national guidelines for high-risk clinics in those countries. The Cambridge group response is representative of the recommended guidelines in East Anglia and broadly in keeping with the NICE guidelines in the rest of the UK. The Spanish response represents the recommended practices in the Catalan Institute of Oncology network hospitals in Catalonia. The Canadian response reflects their Provincial guidelines. Naturally, it is beyond the scope of the current study to ensure that these guidelines and recommendations are being followed in practice in every high-risk clinic in these countries and regions. The respondents all are affiliated with high-risk clinics and have been actively

involved in the follow up of women at increased risk of developing breast/ovarian cancer since the late 1990s.

Surveillance schemes prior to risk reducing surgery

Breast cancer

Table 1 displays the recommended surveillance schemes at the various centers and the guidelines that form the basis of these schemes. As is evident from the table, the NCCN guidelines play a major role in directing practices in high-risk clinics in the USA as well as in Spain and Hong Kong. Similarly, the NICE guidelines are used in the UK. The Dutch, Catalans, Austrian, Belgian, German, Polish, Danish, Swedish, and Australian respondents base their practices and protocols on published or established national and regional guidelines developed from published data. Physician-guided clinical breast exam (CBE) is almost unanimously part of the surveillance regime (except in Italy, Adelaide, and Cambridge) mainly starting as of 20–25 years (but as early as of 18 years in Austria and Hong Kong), and is performed once or twice a year. Magnetic Resonance Imaging (MRI) of the breasts is offered annually predominantly starting at 25 years of age, whereas in Cambridge (UK), Italy, and Australia this modality of breast imaging starts at age 30 years. In the Polish center and Sweden, MRI alternating with breast sonography is performed every 6 months. Breast MRI is offered starting at 18 years of age in Hong Kong (as part of a research protocol). Notably 11 of the 22 centers surveyed had no upper age limit of performing a MRI, whereas in 11 centers the upper age limit for breast MRI widely varied between 50 and 80 years, the latter mostly depending on the overall health status of the mutation carrier, her breast density and/or life expectancy, and in Australia, MRI is not funded for women over 50 years of age. Use of mammography as a screening tool is also advocated. This modality is offered starting primarily from 30 years of age, but is offered starting at 25 years of age (Hong Kong, and in 2 US centers), 35 years (Korea, Spain, Austria, Israel), and 40 years (Belgium, Germany, Italy). Most centers (n=15) had no upper age limit for mammography, while the upper age limit ranged from 69–80 years in the other centers. If both breast imaging modalities are used, this is being done in an alternating mode, so that every 6 months breast imaging is performed.

Ovarian cancer

Table 2 displays the recommended and practiced surveillance schemes for possible detection of ovarian/fallopian tube cancer. As is evident from the table, most centers advocate use of a combined approach that encompasses gynecological exam, transvaginal ultrasound (TVUS) and CA 125 serum level determination once or twice a year from age 18–30 years, until RRSO is implemented. Seven centers (from England, Germany, the Netherlands, Canada, Boston and the two Australian centers) do not advocate any regular surveillance for detecting ovarian/fallopian tube cancer in asymptomatic *BRCA1/BRCA2* mutation carriers, due to lack of any proven effective scheme to facilitate *bona fide* early detection of this cancer type in any clinically significant manner.

Surveillance schemes after risk reducing surgery

Breast cancer

Following RRM most centers surveyed still propose breast exam either as a monthly self-exam (e.g., Sweden, UK, the Netherlands) or a semi- annual or annual physician/health professional guided CBE (e.g., Poland, Germany, Hong Kong, Belgium, three US centers, both Australian centers, and Catalonia). In Austria and Israel, post RRM surveillance scheme includes annual MRI and ultrasound (US) with no upper age limit. The use of annual breast MRI is advocated by the Catalan group until age 50 years if nipple preservation has been performed. In Germany, Korea, and Los Angeles a post-surgical MRI is performed to assess how much residual breast tissue is remaining, especially when nipple sparing mastectomy is performed. Use of annual MRI surveillance is then individualized in these centers and complemented by breast US, if necessary.

Ovarian cancer

In all but 5 centers there are no suggested and/or practiced recommendations for detection of primary peritoneal carcinomatosis after RRSO, and women are no longer being examined by a gynecologist beyond the recommendations for the general, average risk population. In Austria, Poland, and Israel the pre- and post-RRS surveillance schemes are identical, except that in Israel the TVUS and pelvic exam are performed once a year (rather than once every 6 months). In Belgium, mutation carriers are offered an annual pelvic exam, and in Los Angeles (CSMC), annual pelvic exams and CA 125 determinations are being offered, especially if the uterus has been left in situ.

Discussion

The current survey reveals that surveillance schemes for early detection of breast cancer in BRCA mutation carriers who have not undergone RRM, are primarily based on a combination of CBE and a breast imaging modality at predetermined intervals in all participating centers. However, there are wide variations in some of the parameters of the screening scheme: age at start of intensified screening, the upper age limit (if any), timing of incorporating mammograms, and the frequency of breast imaging use. There is a growing body of evidence supporting use of annual screening MRI in this high-risk population, and this is becoming common practice in countries where the facilities are available and reimbursable by health insurers [16–18]. The value of MRI as a screening modality for breast cancer in high-risk women and specifically in BRCA mutation carriers, is hampered by the significant financial burden it imposes on the health care system, compared with mammography. However, breast MRI combined with mammography has been shown to be cost effective in *BRCA1* and (to a lesser extent) in *BRCA2* mutation carriers [19, 20]. Annual mammography is associated with cumulative ionizing radiation exposure, which, in *BRCA1* and *BRCA2* mutation carriers has been suggested to increase breast cancer risk [21], though this possible risk has not been conclusively accepted [22], or replicated [23]. The combined impact of the above mentioned factors is reflected by the wide variability in the specific surveillance schemes offered in the various centers. All centers (except those in the UK, Italy, and the two Australian centers) offer annual breast MRI starting at 25 years of

age, while in Hong Kong breast MRI is offered annually from age 18, as part of a research protocol, though there is no evidence to support MRI prior to 25 years of age. In most centers (Table 1) between 30–50 years of age, MRI alternating with mammography is offered, so that every 6 months breast imaging modality is performed. In Germany, Belgium, and Italy, mammography is only incorporated into the scheme at 40 years of age. Another point of variability concerns the upper age limit of any type of breast imaging. MRI is performed up to 50 years of age in Italy, the UK, and Australia, while this is carried out until 60–65 years in the Netherlands and Canada, and up to older age or with no age limit in the other centers. Regarding mammography, the upper age limit is higher than that used for MRI, but still variable, and in some centers (e.g., UK, Belgium) the upper age limit is 69–80 years depending on the predicted life expectancy and the overall health status of the woman.

The use of breast sonography as an additional modality for breast cancer screening tool is not recommended or practiced by most centers, while in some (e.g., Israel and MSKCC), it is being used during pregnancy and breast feeding at 3 month intervals, as the sole breast imaging modality. The disenchantment with breast ultrasonography is based on several large scale studies that have shown the lack of utility of this modality as an effective screening tool specifically in high-risk populations [24].

In 7/22 centers, screening for detection of ovarian/fallopian tube cancer is either not offered at all or alluded to but not recommended. In the other centers, the surveillance schemes from age 18–35 years consist of clinical gynecological exam combined with serum CA125 measurements and TVUS. One of the major challenges to developing an effective screening strategy for ovarian/fallopian tube cancer has been the requirement of a very high specificity. Unlike with breast cancer, where a biopsy can be performed for diagnosis, in ovarian cancer the malignant lesions may be totally missed by clinical exam and/or TVUS, and suspicious lesions require invasive surgery and removal of the ovaries to make a definitive diagnosis and determine staging. Therefore, any screening strategy for ovarian cancer must have an exceptionally low false positive rate in order to achieve a low and acceptable number of unnecessary operations per screen detected case. A recent study from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) group reported that the sensitivity for early stage disease increased from a historical baseline of 20% under standard care to almost 50% using a 2-stage screening strategy involving serial CA 125 biomarker measurement [25], and the mature results indicate that this translates into improved mortality from ovarian cancer under specific circumstances [26]. While the initial results from the UKTOCS trial are encouraging, this was a trial of average risk women; the results from their sister trial in high-risk women [https://www.ucl.ac.uk/instituteforwomenshealth/womens-cancer/gcrc/ukfocss] and the GOG 19–9 trial [27], that focused on high-risk women are awaited with interest. The current lack of evidence in support of ovarian cancer screening in high risk women, the rate of subsequent investigations required by women undertaking screening, and the fact that the outcome of screening trials in this high group is awaited, should be discussed with each mutation carrier.

Overwhelmingly most centers do not offer any specific surveillance schemes for BRCA mutation carriers who have undergone RRM and RRSO, primarily since the residual annual risk of breast and/or ovarian/peritoneal cancer is low after RRS, often at levels lower than

the general population risk [3, 28]. Moreover, there are no validated data from prospective, long term follow up studies to support offering such schemes. The few centers that do offer breast cancer detection scheme limit these recommendations to CBE and when residual breast tissue is deemed “significant” or when nipple sparing surgery is performed (e.g., Spain, Los Angeles) or regardless of that (e.g., Austria, Israel) annual MRI and breast sonography (Israel) are offered. Following RRSO routine, non-intensified gynecological care is advocated by most centers, similar to the routine gynecological care offered to average risk population. There are a paucity of data on the use of serial CA 125 level measurements as a tool in high-risk women post RRSO, similar to what has been reported for average risk women [25]. Currently there is no compelling reason to maintain active early detection surveillance schemes for breast and ovarian cancer for women post RRS.

There are several limitations to this study. First and foremost this is not a comprehensive evaluation of the practices in all participating countries. There was no attempt to verify the actual adherence of women to any of the suggested schemes as well as the success rate of the various strategies in detecting cancer at early stages. Furthermore, only 34% of the addressed representatives responded to this survey. However, these included representatives of the major continents and countries involved in identifying and caring for high-risk women for many years, who apply local and national guidelines that are evidence based. Additionally, no scheme that pertains to specific conditions such as pregnancy and breast feeding was assessed, no distinction was attempted to discern between surveillance for nipple sparing versus non-nipple conserving mastectomy, and the guidelines only apply to cancer free women and may be altered if these women are breast or ovarian cancer survivors.

In conclusion, based on the results of this most comprehensive effort to date to capture the recommended surveillance schemes offered to asymptomatic BRCA carriers globally, there seems to be broad agreement within the surveyed centers that a surveillance scheme for early detection of breast cancer from an early age (mostly 25–30 years) based on CBE and breast imaging by MRI and complemented with mammography at a somewhat older age, should be recommended. Yet, several distinct inter- center differences are apparent: the upper age limit of MRI and/or mammography, age of incorporating mammography into the surveillance scheme, and optimal surveillance frequency. After RRM, some centers continue to offer some form of breast imaging. In addition, while the overwhelming majority of participating centers agree that no active surveillance should be offered to BRCA mutation carriers after RRS, disagreement on the use of and recommendations for ovarian/fallopian tube cancer surveillance scheme prior to RRS is evident. Surveillance regimens regarding detection of ovarian/fallopian tube cancer, if performed, should therefore be done in the context of clinical studies. Clearly, additional research is warranted to obtain more data on the efficacy of the different surveillance schemes and the outcome after RRM and RRSO for cancer free *BRCA* mutation carriers. These efforts should provide evidence on actual impact of the surveillance schemes on morbidity and mortality from cancer, without a negative impact on morbidity and mortality from the screening process itself. To that end, a multinational collaborative effort targeting BRCA mutation carriers in high-risk clinics globally is warranted.

Acronyms of participating centers

BIDMC	Beth Israel Deaconess Medical Center, Boston, MA
CSMC	Cedars Sinai Medical center, Los Angeles, CA
GC-HBOC	German Consortium-Hereditary Breast Ovarian Cancer
ICO	Catalan Institute of Oncology, Barcelona, Catalonia
IHCC	International Hereditary Cancer Centre
KOHBRA	Korean Hereditary Breast Cancer Study
MDACC	MD Anderson cancer center, Houston, TX
MSKCC	Memorial Sloan Kettering cancer Center, New York City, NY
PENN	University of Pennsylvania, PA
SWE-BRCA	Swedish Breast cancer study

References

1. Nelson HD, Pappas M, Zakher B, Mitchell JP, Okinaka-Hu L, Fu R. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2014; 160(4):255–266. [PubMed: 24366442]
2. Armstrong AC, Evans DG. Management of women at high risk of breast cancer. BMJ. 2014; 348:g2756.doi: 10.1136/bmj.g2756 [PubMed: 24778341]
3. Marchetti C, De Felice F, Palaia I, Perniola G, Musella A, Musio D, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Women's Health. 2014; 14:150–157. DOI: 10.1186/s12905-014-0150-5 [PubMed: 25494812]
4. Walker JL, Powell CB, Chen LM, Carter J, Bae Jump VL, Prker LP, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer. 2015; 121:2108–2120. DOI: 10.1002/cncr.29321 [PubMed: 25820366]
5. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. J Clin Oncol. 2005; 23(34):8629–8635. [PubMed: 16314625]
6. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010; 304(9):967–975. DOI: 10.1001/jama.2010.1237 [PubMed: 20810374]
7. Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014; 32(15):1547–1553. DOI: 10.1200/JCO.2013.53.2820 [PubMed: 24567435]
8. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collée JM, van Doorn HC, et al. Hereditary Breast and Ovarian Cancer Research Group Netherlands. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst. 2015; 107(5) pii: djv033. doi: 10.1093/jnci/djv033
9. Pruthi S, Heisey RE, Bevers TB. Chemoprevention for Breast Cancer. Ann Surg Oncol. 2015; 22(10):3230–3235. DOI: 10.1245/s10434-015-4715-9 [PubMed: 26202562]
10. Chai X, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Use of risk-reducing surgeries in a prospective cohort of 1,499 BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2014; 148(2):397–406. DOI: 10.1007/s10549-014-3134-0 [PubMed: 25311111]

11. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009; 101(2):80–87. DOI: 10.1093/jnci/djn442 [PubMed: 19141781]
12. Finkelman BS, Rubinstein WS, Friedman S, Friebel TM, Dubitsky S, Schonberger NS, et al. Breast and ovarian cancer risk and risk reduction in Jewish BRCA1/2 mutation carriers. J Clin Oncol. 2012; 30(12):1321–1328. DOI: 10.1200/JCO.2011.37.8133 [PubMed: 22430266]
13. Ponder BA. Setting up and running a familial cancer clinic. Br Med Bull. 1994; 50(3):732–745. [PubMed: 7987652]
14. Bancroft EK, Locke I, Ardern-Jones A, D'Mello L, McReynolds K, Lennard F, et al. The carrier clinic: an evaluation of a novel clinic dedicated to the follow-up of BRCA1 and BRCA2 carriers--implications for oncogenetics practice. J Med Genet. 2010; 47(7):486–491. DOI: 10.1136/jmg.2009.072728 [PubMed: 20472659]
15. Pichert G, Jacobs C, Jacobs I, Menon U, Manchanda R, Johnson M, et al. Novel one-stop multidisciplinary follow-up clinic significantly improves cancer risk management in BRCA1/2 carriers. Fam Cancer. 2010; 9(3):313–319. DOI: 10.1007/s10689-010-9333-x [PubMed: 20300867]
16. Knuttel FM, Menezes GL, van den Bosch MA, Gilhuijs KG, Peters NH. Current clinical indications for magnetic resonance imaging of the breast. J Surg Oncol. 2014; 110(1):26–31. DOI: 10.1002/jso.23655 [PubMed: 24861355]
17. Bick U. Intensified surveillance for early detection of breast cancer in high-risk patients. Breast Care (Basel). 2015; 10(1):13–20. DOI: 10.1159/000375390 [PubMed: 25960720]
18. Mann RM, Balleyguier C, Baltzer PA, Bick U, Colin C, Cornford E, et al. European Society of Breast Imaging (EUSOBI). The European Breast Cancer Coalition. Breast MRI: EUSOBI recommendations for women's information. Eur Radiol. 2015; 25(12):3669–3678. DOI: 10.1007/s00330-015-3807-z [PubMed: 26002130]
19. Cott Chubiz JE, Lee JM, Gilmore ME, Kong CY, Lowry KP, Halpern EF, et al. Cost-effectiveness of alternating magnetic resonance imaging and digital mammography screening in BRCA1 and BRCA2 gene mutation carriers. Cancer. 2013; 119(6):1266–1276. DOI: 10.1002/cncr.27864 [PubMed: 23184400]
20. Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA. 2006; 295(20):2374–2384. [PubMed: 16720823]
21. Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Noguès C, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ. 2012; 345:e5660.doi: 10.1136/bmj.e5660 [PubMed: 22956590]
22. Haffty BG, Lee C. Exposure to diagnostic levels of radiation prior to age 30 increases the risk of breast cancer in BRCA1/2 carriers. Evid Based Med. 2013; 18(4):e40.doi: 10.1136/eb-2012-101075 [PubMed: 23220468]
23. Giannakeas V, Lubinski J, Gronwald J, Moller P, Armel S, Lynch HT, et al. Mammography screening and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a prospective study. Breast Cancer Res Treat. 2014; 147(1):113–118. DOI: 10.1007/s10549-014-3063-y [PubMed: 25082516]
24. Riedl CC, Luft N, Bernhart C, Weber M, Bernathova M, Tea MK, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol. 2015; 33(10):1128–1135. DOI: 10.1200/JCO.2014.56.8626 [PubMed: 25713430]
25. Menon U, Ryan A, Kalsi J, Gentry-Maharaj A, Dawnay A, Habib M, et al. Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015; 33(18):2062–2071. DOI: 10.1200/JCO.2014.59.4945 [PubMed: 25964255]
26. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2015; pii: S0140-6736(15):1224–1226. doi: 10.1016/S0140-6736(15)01224-6

27. Greene MH, Piedmonte M, Alberts D, Gail M, Hensley M, Miner Z, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. Cancer Epidemiol Biomarkers Prev. 2008; 17(3):594–604. DOI: 10.1158/1055-9965.EPI-07-2703 [PubMed: 18349277]

28. Heemskerk-Gerritsen BA, Menke-Pluijmers MB, Jager A, Tilanus-Linthorst MM, Koppert LB, Obdeijn IM, et al. Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis. Ann Oncol. 2013; 24(8):2029–2035. DOI: 10.1093/annonc/mdt134 [PubMed: 23576707]

29. Singer CF, Tea MK, Pristauz G, Hubalek M, Rappaport C, Riedl CC, et al. Clinical Practice Guideline for the prevention and early detection of breast and ovarian cancer in women from HBOC (hereditary breast and ovarian cancer) families. Wien Klin Wochenschr. 2015; 127(23–24): 981–986. DOI: 10.1007/s00508-015-0880-x [PubMed: 26525377]

30. Robays, J., Stordeur, S., Hulstaert, F. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2015. Oncogenetic testing and follow-up for women with familial breast/ovarian cancer, Li-Fraumeni syndrome and Cowden syndrome. KCE Reports 236. https://kce.fgov.be/sites/default/files/page_documents/KCE_236_oncogenetictesting_Report.pdf

31. Meindl A, Ditsch N, Kast K, Rhiem K, Schmutzler RK. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011; 108(19):323–330. [PubMed: 21637635]

32. Llort G, Chirivella I, Morales R, Serrano R, Sanchez AB, Teulé A, et al. SEOM Hereditary Cancer Working Group.- SEOM clinical guidelines in Hereditary Breast and ovarian cancer. Clin Transl Oncol. 2015; 17(12):956–961. DOI: 10.1007/s12094-015-1435-3 [PubMed: 26669313]

Table 1

Pre RRS breast cancer surveillance schemes

Country	Center	Breast exam Start age/end age/Times/ year	MRI Start age/end age/Times/ year	US Start age/end age/Times/year	Mammo Start age/end age/ Times/year	Guidelines	Comments
USA	CSMC	25/No[1]/2	25/No/1[2]	None	25/No/1[2]	NCCN	
USA	MSKCC	25/No/2	25/No/1[2]	None *	25/No/1[2]	NCCN	US offered during pregnancy & breastfeeding
USA	MDACC	25/No/2	25/75/1[2]	None	30/No/1[2]	NCCN	
USA	PENN	25/No/2	25/No/1[2]	None	30/No/1[2]	NCCN	
USA	BIDMC	25/No/2	25/No/1	None	30/No/1	NCCN	
USA	Utah	20/No/2	25/Breast density dependant/1	None	30/No/1	NCCN	
Canada	British Columbia	25/No/1–2	25/65/1[2]	None	30/No/1[2]	Self developed	
Austria	Vienna	18/No/1	25/No/1[2]	None	35/No/1[2]	National guideline [29]	
Belgium	Ghent	20–25/70–80/2	25/70–80/1	25/70–80/1	40/70–80/1	KCE report [30]	[3]
Denmark	Copenhagen	30/70/1	25/70/1	30/70/1	30/70/1	National Guidelines	[4]
England	Cambridge	As required	30/49/1[2]	None	30/69/1[2]	NICE GC 164	
Germany	Cologne	25/No/2	25/70/1[2]	25/70/1–2	40/70/1[2]	GC-HBOC[4] (AWMF guidelines [31]	[5]
Netherlands	Rotterdam	25/60/1	25/60/1	None	30/75/1	National guidelines	[6]
Italy	Genoa	As required	30/50/1	None (unless MRI is contraindicate)	40/No/1	Regional	MRI >50–as required
Poland	IHCC, Szczecin	25–30/No/2	25–30/No/1	30/No/1[5]	30/No/1	National Guidelines	[8]
Spain	ICO	25/No/2	25/50–70/1	25/35–70/1	35/70/1	ICO, NCCN, SEOM [32]	Imaging ages and modality depend on breast density
Sweden	SWE-BRCA	25/No/1	25/55–60/1[7]	25/No/1[7]	30/No/1[2]	National Guidelines	Monthly self breast exam; Earlier than 25 if cancer cases <30
Australia	Sydney	30/No/1	30/50/1[2]	None	30/No/1[2]	EviQ.org.au	
Australia	Adelaide	women should be “breast aware”	30/50/1[2]	None	30/No/1[2]	EviQ.org.au	

Country	Center	Breast exam Start age/end age/Times/ year	MRI Start age/end age/Times/ year	US Start age/end age/Times/year	Mammo Start age/end age/ Times/year	Guidelines	Comments
China	Hong Kong	18/No/2	18/No/1[2]	18/No/1[2]	25/No/1[2]	NCCN	
Korea	KOHBRA	25/No/2	25/No/1	None	30/No/1	Self developed	National Guidelines
Israel	SMC	25/No/2	25/No/1[2]	25/No/1[2]	35/No/1[2]	Self developed	

[1] No – No upper age limit

[2] Alternating MRI with mammogram- one breast imaging every 6 months

[3] Before 40 yrs of age: MRI alternating with US (1 exam/6 months); from 40 years of age onwards: MRI alternating with mammography +US (1 exam/6 months); Currently considering removing US from screening program- KCE report - https://kce.fgov.be/sites/default/files/page_documents/KCE_236_oncogenetictesting_Report.pdf

[4] Above age 70 - breast exam and mammogram every 2 years

[5] Before 40 years of age: MRI (annual) and US (semiannual); from 40 years of age onwards: MRI (annual) and mammography (every 2 years) and US (semiannual)- AWMF guidelines- http://www.awmf.org/uploads/tx_szleitlinien/032-045OL_l_S3__Brustkrebs_Mammakarzinom_Diagnostik_Therapie_Nachsorge_2012-07.pdf

[6] In case of annual MRI and mammography: being done either at the same time, or in an alternating schedule

[7] Alternating- breast imaging by MRI/US once a year

[8] Alternating MRI with US - one breast imaging every 6 months between 25–30 y, and after 30y US when necessary if mammographic dense breast

Table 2

Pre RRS Ovarian cancer surveillance schemes

Country	Center	Gyn exam Start age/end age/Times/ year	CA 125 Start age/end age/ Times/year	US Start age/end age/ Times/year	Guidelines	Comments
USA	CSMC	25/No/2	25/No/2	25/No/2	NCCN	
USA	MSKCC	30–35/No/2	30–35/No/2	35/No/2	NCCN	Earlier for BRCA1 carriers
USA	MDACC	35/No/1–2	35/No/2	35/No/2	NCCN	
USA	PENN	30/No/1	30–35/No/1–2[1]	30–35/No/1–2[1]	NCCN	Earlier for BRCA1 carriers
USA	BIDMC	None	None	None	NCCN	
USA	Utah	None	35/no/1–2	35/no/1–2	NCCN	
Canada	British Columbia	None	None	None	Self developed	Not advised – actively discouraged
Austria	Vienna	18/No/1	35/No/1	35/No/1	National guideline [29]	CA 125 and TVUS offered not recommended
Belgium	Ghent	35/70–80/2	35/70–80/2	35/70–80/2	Self-developed	
Denmark	Copenhagen	30/N0/1	30/N0/1	30/N0/1	National guidelines	
England	Cambridge	None	None	None	National consensus	
Germany	Cologne	None	None	None	GC-HBOC (AWMF guideline [31]	
Netherlands	Rotterdam	35/No/Once	35/No/Once	35/No/Once	National guidelines	CA 125 and TVUS offered not recommended 2
Italy	Genoa	30/No/2	30/No/2	30/No/2	Regional	CA 125 and TVUS offered not recommended
Poland	IHCC, Szczecin	30–35/No/1	30–35/No/1	30–35/No/1	National guidelines	
Spain	ICO	35/70/1	35/70/1	35/70/1	ICO, NCCN, SEOM [32]	
Sweden	SWE-BRCA	30/No/1	None	30–35/No/1	National guidelines	
Australia	Sydney	None	None	None	EviQ.org.au	
Australia	Adelaide	None	None	None	EviQ.org.au	
China	Hong Kong	18/No/1	18/No/1	18/No/1	NCCN	
Korea	KOHBRA	35/No/2	35/No/2	35/No/2	Self-developed	National Guidelines
Israel	SMC	25/No/2	25/No/2	25/No/2	Self developed	

[1]Yearly 30–35 then twice yearly

[2] A single visit to provide detailed information on the lack of efficacy of gynecological surveillance, and the advice to consider RRSO as of 35–40 years for BRCA1, and of 40–45 years for BRCA2 mutation carriers 27