Imaging surveillance programs for women at high breast cancer risk in Europe: Are women from ethnic minority groups adequately included? (Review)

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Abstract. Women from ethnic minority groups, including immigrants and refugees are reported to have low breast cancer (BC) screening rates. Active, culturally-sensitive outreach is vital for increasing participation of these women in BC screening programs. Women at high BC risk and who belong to an ethnic minority group are of special concern. Such women could benefit from ongoing trials aimed at optimizing screening strategies for early BC detection among those at increased BC risk. Considering the marked disparities in BC survival in Europe and its enormous and dynamic ethnic diversity, these issues are extremely timely for Europe. We systematically reviewed the literature concerning European surveillance studies that had imaging in the protocol and that targeted women at high BC risk. The aim of the present review was thereby to assess the likelihood that women at high BC risk from minority ethnic groups were adequately included in these surveillance programs. Twenty-seven research groups in Europe reported on their imaging surveillance programs for women at increased BC risk. The benefit of strategies such as inclusion of magnetic resonance imaging and/or more intensive screening was clearly documented for the participating women at increased BC risk. However, none of the reports indicated that sufficient outreach was performed to ensure that women at increased BC risk from minority ethnic groups were adequately included in these surveillance programs. On the basis of this systematic review, we conclude that the specific screening needs of ethnic minority women at increased BC risk have not yet been met in Europe. Active, culturally-sensitive outreach is needed to identify minority women at increased BC risk and to facilitate their inclusion in on-going surveillance programs. It is anticipated that these efforts would be most effective if coordinated with the development of European-wide, population-based approaches to BC screening.

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Abbreviations: CBE, clinical breast examination; CE, contrast enhanced; MARIBS, magnetic resonance imaging for breast cancer screening study (UK); MRI, magnetic resonance imaging; MRISC, multicenter MRI screening study (The Netherlands); PIMMS, psychological impact of mammography screening in women with family history of breast cancer (UK); STIC IRM, magnetic resonance imaging study group (France)

Key words: breast cancer, early detection, imaging surveillance, BRCA mutations, cultural sensitivity, ethnicity

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1. Breast cancer survival disparities, ethnicity and related issues for Europe

Breast cancer is the most commonly diagnosed malignancy and a leading cause of cancer deaths among women in Europe (1,2). Survival after diagnosis of breast cancer varies markedly across Europe; this is attributed to differences in stage at diagnosis (3). Early breast cancer detection can be achieved through screening which, when followed by appropriate assessment and management, has been demonstrated to significantly reduce mortality from breast cancer (4,5).

The importance of screening has been particularly emphasized for women with high breast cancer risk, for whom there is a greater likelihood of more aggressive tumors presenting at a younger age (6-8). Intensive screening using various imaging modalities is reportedly tolerated and preferred by women at high risk, compared to options such as prophylactic mastectomy (9,10). Many investigations have focused upon finding the best strategies for screening surveillance of women with high breast cancer risk (11,12). In the UK women at very high risk of familial breast cancer are being offered annual surveillance with magnetic resonance imaging from age 30 to 49 years and annual mammography from the age of 40-69 (13).

A critical challenge is to effectively identify women from the general population who are at high risk for breast cancer, so that they can benefit from these more intensive screening surveillance strategies. Breast cancer risk assessment models have been based upon family history, including age of disease onset. However, it has been reported that relying on family history can be tenuous, especially for identifying *BRCA*1/2 mutation carriers (14-16).

Certain ethnic groups within Europe are recognized to have a high prevalence of *BRCA1/2* mutations; these include Ashkenazi Jewish, Icelandic and Inuit groups, inter alia (5,17,18). Founder *BRCA*1/2 mutations (founders are fairly small groups of people who have been somewhat isolated over long periods of time, such that a mutation which would otherwise have been rare becomes relatively common within the population) have been identified for these groups, as well as for other European populations including, for example, Norwegians, Finns, Swedes, Dutch, Calabrians and Sardinians from Italy (19) as well as among Slavic people (20). In addition, founder *BRCA*1/2 mutations have been detected for several other ethnic groups whose members have immigrated to Europe. Among these groups are Pakistanis, Malaysians, Hispanics from Colombia, Japanese, Chinese and Sephardic Jews from several Arab countries (19,21). It has been suggested that testing for *BRCA*1/2 should be considered for much less significant family history among founder populations (13), and that population screening for BRCA mutations may be an appropriate alternative for such populations (22). On the other hand, among ethnic groups in Europe with overall low breast cancer risk, the relative percentage of aggressive cancers appearing among young patients may be very high, as is reported among North African populations living in France (23).

It is also important to take into account small family size, 'limited family structure' (24) when assessing breast cancer risk, especially when there are few middle-aged or older female family members. Since the BRCA breast and ovarian cancer syndrome has an autosomal dominant inheritance, ~50% of the mutation carriers will be male. Especially insofar as the number of female 1st and 2nd degree relatives above age 45 is small, with a limited family structure, the likelihood of accurately predicting BRCA mutation carrier status in single cases of early-onset breast cancer may be substantially diminished (25-27).

Lower breast cancer screening rates and consequent late stage diagnosis have been frequently associated with ethnic minority groups. This is particularly the case for women who are economically deprived and/or immigrants or refugees (28-36). Women from ethnic minority groups who are at high breast cancer risk are thus of particular concern. A critical question is whether these women are adequately included in ongoing screening programs aimed at women with high breast cancer risk. Given Europe's enormous ethnic diversity and the influx of residents from the entire world, in addition to the marked disparities in breast cancer survival, these issues are extremely timely.

In our earlier review performed through 2008 (34), we identified breast cancer surveillance studies of high-risk women from fifteen European centers that had imaging in their protocols. Our focus therein was on the Jewish population as a high-risk group. Our conclusion at that time was that the imaging surveillance was beneficial, but that Jewish women and other ethnic minority groups at potentially high risk were unlikely to have been adequately included in these programs.

The aim of the present study is to systematically review the published literature from Europe, through the more recent period (end of 2014), on breast cancer surveillance studies that had imaging in the protocol and that targeted women at high-risk for breast cancer. Our research focus is broadened in the present study to assess the likelihood that women from diverse minority ethnic groups were adequately included in these surveillance programs. The overall purpose of this review is to identify ways of diminishing the disparities in breast cancer survival in Europe.

2. Search strategy for identifying European imaging surveillance studies targeting women at high breast cancer risk

We sought empirical studies based in Europe, which targeted women at high risk for breast cancer, and which had imaging as part of the surveillance protocol. The latter included more frequent mammography screening intervals, younger age of onset for mammography, use of magnetic resonance imaging (MRI) and/or ultrasound. Studies were excluded if only persons already diagnosed with breast cancer were examined or if imaging was only used for evaluating previously detected lesions.

We began with Ovid Medline using the search terms as key words plus the 'explode' option. This was performed as follows: [(breast cancer) AND (high risk) AND {(ultrasound) or (mammography) or (magnetic resonance imaging)}]. Altogether, 1024 possibly eligible studies were identified. A PubMed search was then done, using the following strategy: [{(surveillance) or (early detection)} and (high risk) and (breast cancer)]. This yielded another 260 potentially eligible studies. We also searched PubMed through the strategy: [{(breast cancer)} AND (high risk) AND {(Europe) or (Scandinavia) or any of (42 European country names)}], finding another 90 potentially eligible studies. These searches were performed through December 2014. The abstracts and/or full-text studies were then reviewed. Relevant cited studies were accessed for needed background information.

Altogether we identified 27 different European study centers that fulfilled the above-described criteria. One or more studies were found that reported empirical data about these surveillance programs. There was a total of 62 such studies (37-46,50-67,70-74,76-82,84-87,91-93, 95-96,99-102,106,107,110-112,120,121,123,126). In addition, another 30 studies provided background information about the Study Centers (47-49,68,69,75,83,88-90,94,97,98, 103-105,108,109,113-119,122,124,125).

3. Protocol for reviewing the identified surveillance studies

For each of the 27 surveillance programs, an independent review was performed by two investigators. Basic information was summarized, including the imaging modalities used, number of cases detected and benefit of the trial. The studies were scrutinized to ascertain how participants were recruited, as well as criteria for entry into the study. Next, the studies were examined to determine whether a) there was any note of ethnic minority groups at high risk for breast cancer, and if so, b) whether these groups were taken into account in the actual risk assessment and recruitment. Each reviewer also assessed whether the studies considered: c) the possibility of limited family structure and d) family members living outside the country.

On the basis of points a) through d) together with consideration of the entry criteria and recruitment procedure, each of the 27 study centers was given an overall assessment rating concerning the likelihood of adequately including minority ethnic women at high breast cancer risk in the study catchment area.

This overall assessment was scored as follows: 3, Active surveillance with a very high participation rate of the entire at-risk minority population in the catchment area; adequate account taken of eventual limited family structure and family living outside the country. 2, Systematic efforts were made to include at-risk minority populations, but the study center unlikely to have achieved sufficiently high coverage to do so. 1, Although not taken into account for recruitment, high-risk ethnicity and/or limited family structure and/or family members living outside the country were factors considered in the study design. 0, No attention whatsoever to high-risk ethnicity nor to limited family structure nor to family members living outside the country. Recruitment procedure and entry criteria render it very unlikely that women at high breast cancer risk who are from ethnic minority groups were included in the program.

The scores were additive, such that each study was credited for all actions that could have increased the likelihood of adequately detecting and including women from minority ethnic groups at high breast cancer risk within the catchment area. Fractional scores to the 0.25 level were permitted. Insofar as the two reviewers could not arrive at consensus, a third served as arbiter. Arbitration was needed for two of the 27 study groups.

4. General description of the 27 identified European study centers

Table I summarizes the pertinent considerations about each of 27 study centers. The centers are sorted by country, and each was assigned an identification number for the purpose of our assessment.

We begin with the Netherlands where one of the largest prospective investigations was performed among 2157 women. This was the Dutch Multicenter MRI Screening Study (MRISC), denoted as Study Center #1 (37-46). In the MRISC, biannual clinical breast exam (CBE), annual contrast enhanced (CE) MRI and mammography were performed in most cases. The other two Study Centers from the Netherlands (50,51) also applied CBE, CE-MRI and mammography, and in Study Center #2 (50) ultrasound was used in some cases.

Study Centers ##4-10 (52-76) from the UK used various combinations and schedules of mammography, CE-MRI and ultrasound and CBE. The UK Multicentre Study (MARIBS) and the subsequent Nightingale Study (Study Center #4) (52-67) followed altogether 959 women at high risk for up to 7 years with annual CE-MRI and mammography. Study Center #10 (77) from the UK examined women age 35-39 with elevated breast cancer risk who underwent surveillance via annual mammography.

From the German Study Centers (##11-13) (78-85) CBE, CE-MRI, mammography and often ultrasound were also performed. The German Multicenter Study (#11) (78) and the Bonn Center (#12) (79-82) followed 413 and 629 women for up to 6 and up to 10 years, respectively.

The Italian Centers (##14-16) (86-95) also used CBE, CE-MRI, mammography and ultrasound in various combinations. The Italian Multicenter Study (#14) (86,87) included 501 women enrolled between 2000 and 2007 and performed 1592 screening rounds. The Modena Study (#15) (91-93) included 1325 women who were followed for up to 11 years.

There were two Polish Study Centers (##17 and 18) (96-99). The Center from Szczecin (#17) (96-98) provided the majority of 212 women at high breast cancer risk with mammography and in a few cases with MRI, and reported 18 months of follow-up. All 379 women included in the Krakow Center (#18) (99) received MRI, after undergoing mammography and ultrasound that had shown no abnormalities.

The French Study Centers (##19-21) (100-106) used combinations of MRI, mammography and ultrasound. The French Multicenter Study (STIC IRM) (100,101) included 1561 women with a few months of reported follow-up. The Vienna Study Center (#22) (107) included 327 women with up to 7 years of follow-up, using mammography, MRI and ultrasound.

Table I. Breast cancer surveillance studies of women at increased risk in Europe.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk a) Were they noted? If yes, which?	Ethnic Minority Groups at High Risk b) If yes, were they taken into account in risk assessment/ recruitment?	Family History a) Was the possibility of limited family structure taken into account?	Family History b) Were family members living outside the country taken into account?	**Overall Assessment**: Likelihood of adequately including persons from minority ethnic groups at high risk in study catchment area*
#1: DUTCH MULTICENTER MRI SCREENING STUDY (MRISC) den Heijer [37] Essink-Bot [38 Kriege [39-42] [Obdeijn [43] Pieterse [44] Rijnsburger [45] Tilanus-Linthorst [46] Background: Albada [47] Boetes [48] Lammens [49] 2157 women, Prospective Main study: (1999-2006) MRISC-B: 2000-2003, with follow-up in 2007-2009 197 women at increased risk adhering to regular surveillance [37]	In most, but not all cases: biannual CBE, annual CE-MRI, MM ========== 97 BC cases (including 19 DCIS): 78 screen detected (14 DCIS) 13 interval BC (1 DCIS) 6 found at prophylactic mastectomy With both imaging methods at screen: Overall sensitivity: MRI = 71% MM = 41% (MM superior for detecting DCIS, but most markedly poorer for detecting BC in women with BRCA1 mutations) Overall specificity: MRI = 90% MM = 95% Conclusions: MRI more efficient for *BRCA* mutation carriers, generally more sensitive than MM, although MM also detects early cancers missed by MRI. MRI recommended as a standard screening method for BRCA mutation carriers Among the women with detected BC, 6-y survival was high. Intrusion and avoidance lessen over time. Vulnerable women can be identified at an early stage for tailored support [37]	Referred from 6 family cancer clinics Recent data from the Netherlands indicate that 17.3% of counselees had parents born abroad [47]	• Age 25 to 75 unless family member diagnosed < age 30 AND • No previous diagnosis of BC AND • Cumulative lifetime risk > 15% by Modified Claus [35, 36] *Group I* BRCA1/2 or mutation PTEN/TP53 carrier (N=599) *Group II* High Risk (N=1069) --1st degree relative with *BRCA*1/2 mutation --1st degree relative and two other 1st or 2nd degree relatives with BC or OC --Two 1st degree or one 1st and one 2nd degree relative with BC, mean age at diagnosis 45y or younger. *Group III* Moderate Risk (N=489) --2nd degree family member with a *BRCA*1/2 mutation --One 1st degree relative with BC < 40 y. --Two 1st degree relatives or one 1st degree and one 2nd degree relative with BC, mean age at diagnosis 45-60 y. --Three 2nd degree family members with BC or OC --Two 1st degree relatives or one 1st and one 2nd degree relative with BC < age 55 and one with OC In the MRISC-B study, "sufficient understanding of the Dutch language" was an entry criterion (p. 599) [37]	Yes, ↑ risk of BRCA1/2 mutations among Ashkenazi Jewish women & Li-Fraumeni in Brazil. [48]	Importance of ethnic background noted in background article [48] but unclear whether this was actually included in risk assessment and recruitment in MRISC. In the MRISC-B study [37], immigrants may have been excluded by requiring Dutch language proficiency	Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS was taken into account	Not explicitly	**0.75** • Recent data from the Netherlands suggest that a substantial percentage of women referred to counseling centers are from minority ethnic backgrounds/ have parents born outside the country. • High risk ethnic group mentioned in a background publication to the study, though it is unclear whether and if so, how this was actually taken into account in risk assessment and recruitment. • Allowing inclusion based upon single 1st degree relative and allowing for "moderate risk" makes it more likely that LFS was taken into account. Thus, the inclusion criteria may allow for eligibility of a wider circle of women with familial risk. • However, the MRISC-B study may have excluded immigrants by requiring Dutch language proficiency
#2 GRONINGEN Fakkert [50] Background: Albada [47] The Netherlands 139 women (114 without previous BC) Retrospective cohort, median follow-up 2y, 7.2% lost to follow-up (1995–2009)	Annual CBE + annual MM (from age 30) + annual MRI and eventual US (as per protocol, but frequency actually less) ========== 14 BC cases, 60% node positive (2 prevalent, 10 screen detected, 2 interval cases) 21% of MRI and 14% of MM, respectively, led to further workup "The effectiveness of CBE & MM was comparable to earlier findings. MRI screening seemed less effective than earlier findings….After RRSO, the BC risk in BRCA1 and BRCA2 mutation carriers is still high enough to justify intensive BC screening with MRI and MM" (p. 157)[46].	Family cancer clinic UMC Groningen Unaffected women with positive FHx can be referred by primary physician or specialist. Recent data from the Netherlands: 17.3% of counselees had at least one parent born abroad [43]	• BRCA1 or BRCA2 mutation carrier AND • Has undergone risk-reducing salpingo-oophorectomy (RRSO) AND • No history of ovarian cancer AND • ≥ 1 breast eligible for screening AND • Age < 52	No		Not explicitly	Not explicitly	**0.75** • Recent data from the Netherlands suggest that a substantial percentage of women referred to counseling centers are from minority ethnic backgrounds/have parents born outside the country. • However, no description of the actual recruitment procedure for the present study, to ascertain whether there was systematic surveillance of the catchment population, and the minorities therein.

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========= # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		Overall Assessment: Likelihood of adequately including persons from minority ethnic groups at high risk in study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was the possibility of limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#3 ROTTERDAM Tilanus-Linthorst [51] The Netherlands 384 women, age 20 to 74 Prospective (1995-1998)	--Semi-annual CBE, yearly MM --MRI at least once if >50% breast density on MM (109 women) ========== --Of altogether 12 detected BC cases, 3 (all T1N0) were detected by MRI, but were occult on MM & CBE, --6 false positives on MRI Conclusion: MRI considered a promising screening modality for young women at high risk for BC, for whom MM has a lowered sensitivity	Women attending outpatient breast clinic because of family history	>25% risk of BC using Claus criteria (Allows for a single 1st degree relative)	No		Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS was taken into account	Not explicitly	**0.5** • Allowing inclusion on the basis of a single relative makes it more likely that LFS was taken into account.
#4: UK MULTI-CENTRE/ MARIBS & NIGHTINGALE Brown [52-54] Evans [55-57] Gilbert [58] Griebsch [59] Gui [60, 61] Hutton [62] Leach [63, 64] Thompson [65] Tilanus-Linthorst [66] Warren [67] 959 women recruited into the studies Prospective 647 in MARIBS (1997-2004) 312 in Nightingale (2006-2013) Background: Albada [47] Gilbert [68] Leach [69]	Annual CE-MRI and MM ========== 63 BC cases detected in the studies, 37/647 in MARIBS, 26/312 in Nightingale Comparison with 76 BC cases in women at high BC risk receiving intensive MM only, and 557 BC cases in women with BRCA1/2 mutations, but no intensive surveillance [57] MRI was more sensitive than MM, especially for *BRCA*1 mutation carriers, many detected tumors were small & mainly node-negative, but some were large and node positive, possibly related to rapid growth in women with germline mutations MRI estimate of volumetric breast density may predict breast cancer risk in MARIB participants [65] Both MRI and MM were associated with >95% satisfaction and low levels of psychological distress (<15%), but significantly more persistent distress for MRI and less likely to intend to return to MRI than MM. Authors emphasize need for support and "timely information" about the benefits of MRI—and note that most women (88%) intended to re-attend MRI [62] Fewer cancers detected on MRI were node positive (NS compared to MM, p < 0.0001 compared to unscreened. Survival sig. higher in MRI screen vs. no intensive surveillance and intensive vs. no intensive screening [57] Sensitivity 93%, specificity 63% for MRI + MM [57] Conclusion: Recommend annual MRI and MM in this high risk group.	Women recruited through 22 familial BC clinics. Unaffected women with positive FHx can be referred by primary physician or specialist. UK guidelines for referral to breast cancer genetic counseling in [47]: "ethnicity was assessed in accordance with national definitions" altogether 2.1% of counselees considered themselves "other than white British or Irish" Logistic problems and a time lapse were noted to result in women who had consented never actually participating [55]	MARIBS: • 35 – 49 y AND • No previous BC, no other cancer with life-expectancy < 5 y • If genetic testing performed with negative results, excluded from the study AND • Deleterious gene mutation carrier (*BRCA*1/2 or TP53) OR • 1st degree relative of a *BRCA* or TP53 mutation carrier OR • Strong FHx of BC and/or OC, or consistent with classic Li-Fraumeni syndrome (in cases in doubt adjudicated by 3 experts) [64] By strict entry criteria (applied in a sub-study) at least 2 cases needed to be verified by medical record, histology or death certificate [55] AIM: to include women with at least 60% chance of being a *BRCA*1/2 mutation carrier or annual risk at least 0.9% [64] Nightingale: NICE criteria High risk: • 2 1st or 2nd degree relatives with BC < 50 OR • 3 1st or 2nd degree relatives with BC < 60 OR • 4 relatives with BC OR • BC gene identified in a family member OR • 2 1st or 2nd degree relatives with BC or OC plus: --BC < 40 --OC < 50 --BC + OC in same woman --Ashkenazi Jewish ancestry --BC in a male relative --1st or 2nd degree relative with sarcoma < 45}	Ethnicity noted in altogether 1 on the main papers [62]: participants in (MARIBS) were reported to be "97.7% white", 0.2% Pakistani, 1.3% Indian, 0.2% Chinese, 0.6% "other". • Ashkenazi Jewish ethnicity included as a subsidiary risk factor (NICE), but under quite stringent conditions (Nightingale)	Yes, as a subsidiary risk factor, under quite stringent condition (Nightingale)	Not explicitly, adjudicating panel could possibly take LFS into account although no mention that this was done (MARIBS) and by including Ashkenazi Jewish as a criterion, implicitly could be to some extent (Nightingale)	Not explicitly, adjudicating panel could consider family members outside the country, although no mention that this was done. (MARIBS) Requiring verification of family cases would make it difficult to include family members living outside the country (this appears to have been done explicitly in the sub-study using strict entry criteria) (MARIBS)	**1.0** • The adjudicating panel (MARIBS) could have taken ethnicity, LFS & FHx for members outside the country into account, but no mention that this was done. • Requiring verification of family cases (MARIBS) would make it difficult to include family members living outside the country (this appears to have been done explicitly in the sub-study using strict entry criteria) • Non-white ethnic minorities may be underrepresented in the study according to their percentage in the U.K. population (MARIBS) • Ashkenazi Jewish ethnicity subsidiary risk factor, under stringent conditions (Nightingale) • Most recent paper [56] explicitly recognizes the need for "systematic assessment of family history in primary care or through population-based screening [to] identify appreciable numbers of women in their forties, eligible for additional surveillance" p. 993

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment**: Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#5: SOUTH THAMES REGION Murday [70] U.K., 192 women, Prospective (1996 -2001)	Annual MM + CBE (recommended but not full adherence) ========== 9 BC cases (7 visible on MM, 3 of which were non-palpable), all but 1 in those with ≥ 50% chance of carrying a BRCA mutation Conclusion: At least annual screening is important for women at high risk, possibly started before age 35, but maybe unnecessary if low chance of *BRCA*1/2 mutation	Women attending family cancer clinics (61 had > 50% chance of carrying a *BRCA*1 mutation)	• No previous BC AND • < age 50 AND • ≥ One 1st degree relative with BC diagnosed <40 y OR • ≥ 2 relatives < age 60 y with BC (≥ 1 is a 1st degree relative)	No		Not explicitly, requiring only 1 relative with early BC de facto makes it more likely that LFS is taken into account	Not explicitly	**0.5** • Requiring only 1 relative with early BC could make it more likely that LFS was taken into account
#6 NOTTINGHAM Kollias [71] U.K. 1371 women, Prospective, (mean follow-up 22 months) (1988-1995)	Annual CBE, biennial MM, starting 10 y before youngest affected relative ========== 29 cancers (23 invasive, 6 *in situ*) % DCIS sig ↑ with screening compared to age-matched symptomatic women with a positive FHx Conclusion: Young women at increased BC risk may benefit from regular screening which can detect *in situ* lesions	Through a Family History Breast Clinic at the City Hospital	• Below age 50 y AND • Asymptomatic AND • ≥ 1+ affected 1st degree relative below age 60y, or • Multiple affected relatives with onset below age 60 (estimated lifetime BC risk >1/9 Claus)	No		Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS to be included.	Not explicitly	**0.5** • Allowing inclusion on the basis of a single relative makes it more likely that LFS to be included
#7: DUNDEE Reis [72] Scotland, U.K. 8000 annual screens Retrospective (1995-2006)	Annual CBE + MM ========== 46 BC diagnosed in 42 women from the Tayside Programme (34 were detected at screening, 36 were early stage) Compared with: (a) consecutive series of 40 women diagnosed with BC at < 50. (b) 37 affected relatives with BC < 55 y. who had not had access to early screening, 11 had died from BC within 5 y of diagnosis. Conclusion: "Surveillance achieves a beneficial stage shift" with increased survival and decreased treatment costs in about 22% of cases". (p. 319)	Tayside BC Family Clinical Surveillance Programme	Women below age 50 with: Multiple relatives with BC OR A 1st degree relative with BC < age 40 OR Germline BRCA1/2 mutation	No		Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS to be included.	Not explicitly	**0.5** • Allowing inclusion on the basis of a single relative makes it more likely that LFS to be included

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#8: UK Study of annual mammography for younger women with family history of BC, as part of PIMMS = psychological impact of mammography screening in women with family history of BC Brain [73] Tyndel [74] Background Evans [57] 2321 women in cross-sectional analysis [74]. 1286 women in 1 M and 6 M prospective study [73]	MM at 12–18 M intervals ========== Pre-screening cancer worry was the most important predictor of subsequent cancer worry. False-positive screening result was significantly associated with cancer worry at 1M (but not 6M) Among women in the Manchester Breast Cancer Family History Clinic, which has assessed > 9000 women: uptake to MM screening trials for age 35-45 was over 90%, compared to very low uptake for drug & dietary (< 15%) [75]	Referred to specialist clinics by GP or by hospital consultants 21 centers running clinics for family history of breast cancer. Reasons for non-attendance were mainly of a practical nature [74]	Age 35 to 49, no previous BC or FHx of OC AND (NICE guidelines) {Medium risk: • 1 1st degree relative with BC < 40 OR • 2 1st or 2nd degree relatives with BC average age >50 OR • 3 1st or 2nd degree relatives with BC average age >60} OR {High risk: • 2 1st or 2nd degree relatives with BC < 50 OR • 3 1st or 2nd degree relatives with BC < 60 OR • 4 relatives with BC OR • BC gene identified in a family member OR • 2 1st or 2nd degree relatives with BC or OC plus: --BC < 40 --OC < 50 --BC + OC in same woman --Ashkenazi Jewish ancestry --BC in a male relative --1st or 2nd degree relative with sarcoma < 45}	Yes, Ashkenazi Jewish. Broad reference is made to "white ethnic background" without further definition (96% of the cohort)	Yes, as a subsidiary risk factor, under quite stringent conditions	Not explicitly, but by allowing a single family member and by including Ashkenazi Jewish as a criterion, implicitly could be to some extent	Not explicitly	**0.75** • Broad referral system, including primary care would provide a better chance for population coverage. However, the limited information on ethnicity of the participants suggests that few minority/ immigrant women were included in the study. Practical barriers to attendance could contribute. • Ashkenazi Jewish ethnicity included as a subsidiary risk factor, but under quite stringent conditions.
#9: UK National Breast Cancer Screening For Survivors Of Hodgkin's Lymphoma Howell [76] U.K. programme but [Howell 2009] focuses on Greater Manchester & Cheshire Cancer Network, serving 3.2 million people 417 eligible women were invited, 243 (58%) attended screening Retrospective review of screening	25-29 y: Annual MRI ± US 30-50y: Annual MM ± MRI/US >50 y: National Health Service Breast Cancer Screening Programme ========== 23 cases of BC, 5 diagnosed within the surveillance program. None had axillary node involvement compared to 54% of those diagnosed outside the program	Through UK-wide national notification, risk assessment & screening programme—with helpline. Cancer registries – data bases reviewed, telephone helpline & follow-up clinics. Eligible women invited to screening /letters sent to primary care physicians for contact with patients.	--Women treated with supradiaphragmatic RT for Hodgkin's lymphoma before age 36 AND -- (≥ 25 y or ≥ 8 y. post-RT) whichever occurred later	No		Not relevant	Not relevant	0.75 • Wide outreach program unrelated to family BC history makes it more likely that all eligible women in the population would be contacted, except possibly recent immigrants may not be in the registry. The helpline would likely facilitate broader participation. • The difficulties in retrospectively contacting women are noted (42% non-participation)

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#10 Evans [77] U.K. Women age 35 -39 y with lifetime BC risk ≥ 17% who were not receiving MRI screening Prospective analysis from 2010 planned through 2016. As of April 2013, 2280 women were recruited Retrospective analysis from 5 centers "with robust call systems" (1994-2010)	Results available only for retrospective study: MM surveillance ========== 47 BC detected 10 prevalent cases, 22 incident cases, 15 interval cases 26% in situ, 74% < 2cm 25% no nodal involvement for invasive, 91% alive with no distant metastases (all sig superior compared to an unselected surgical series generally sig. superior to unscreened women with a positive family history) Awaiting prospective results "to assess potential added value of digital MM and cancer incidence rates…to inform cost effectiveness analyses"p.13	UK Centers performing MM surveillance of women aged 35-39 y with ↑ BC risk (positive FHx) in 5 centers that record interval cancers 3-generation FHx recorded	Eligibility -1st degree relative with BC < 40 y -1st degree relative with bilateral BC < 50 y -Two 1st degree relatives with BC < 60 y or one 1st degree & one 2nd degree relative with BC < 60y -One 1st or 2nd degree relative with BC and OC < 60 y -Two 1st or one 1st & one 2nd degree female With BC < 60 and OC any age -Three 1st or 2nd degree female with BC or OC any age -One 1st degree male with BC any age -Paternal history of ≥ two 2nd degree relatives with BC < 50 or OC any age or paternal uncle/ grandfather with BC < 50y -BRCA 1 or 2 mutation or ≥ 25% risk of carrying known mutation in the family Exclusion -Inability/refusal to give informed consent -Age < 35y or > 40 y -Hx BC or bilateral mastectomy -Contraindication of annual X-rays -BC detected by MRI but not MM	No		Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS to be included	Not explicitly, but 3 generation history increases likelihood that those outside the country would be included	**0.75** Recruitment procedure/how families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment area and minorities therein Detailed individualized information, allowing various risk levels with inclusion possible based on a single increase chances for women at elevated risk from minority group to participate
#:11 GERMANY MULTI-CENTER (Cologne/ Bonn) Schmutzler [78] 413 women, prospective, (comparison made to detection rates in comparable risk groups under usual surveillance) (1996-2003 for recruitment, followed for 1-6.75 y, median =2.2 y)	Annual MM and dynamic MRI, semi-annual CBE and US ========== 41 BC cases (All screen-detected, 9 DCIS, 1 LCIS, 61% T1, 12% T2, 2% T4. 24 of the invasive BC were node-negative) Significantly more node negative, pre-invasive BC or < 2 cm, compared to BC detected in the control groups outside this surveillance protocol. 41 false positives (5 from MM, 12 from US, 24 from MRI) Conclusion: This multi-modal program was considered to effectively detect early stage BC	By the Familial Breast and OC Center, at both Universities as part of GCHBOC	Fulfilled GCHBOC criteria for genetic testing: {• ≥ 2 relatives with BC in same branch of family diagnosed before age 50, OR • ≥ 1 relative with BC and ≥ 1 relative with OC in same branch of family, OR • ≥ 2 relatives with OC in same branch of family, OR • ≥ 2 relatives with BC in same branch of family, ≥ 1 diagnosed before age 50, OR • ≥ 3 relatives with BC in same branch of family, all diagnosed before age 50, OR • Relative with BC < age 35, OR • Relative with OC < age 40, OR • Male relative with BC, OR • Relative with bilateral BC < age 40} AND • Age 25 – 70 • Not pregnant, lactating, no history of bilateral BC • Normal CBE or MM within 1 y of 1st screening round *Actual participants*: N=49 with proven *BRCA*1/2 mutation, N=203 with high risk (fulfilled one of 1st three criteria) N=161 with moderate risk (fulfilled one of 4th to 9th criteria) N=248 healthy, N=156 with a history of unilateral BC, N=7 with a history of OC, N=2 with a history of BC and OC	No		No, but allowing inclusion based on single 1st degree relative could have this effect to some extent	Not explicitly, but by performing detailed pedigree analysis for 3 or more generations, this may have been facilitated	**0.75** • Actual recruitment procedure/how the families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment population, and the minorities therein. • However, the detailed individualized information and allowing various risk levels may have achieved this to some extent. Inclusion on the basis of a single relative makes it a bit more likely that LFS was taken into account.

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design(Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	High Risk Minority Groups a) Were they noted? If yes, which?	High Risk Minority Groups b) If yes, were they taken into account in risk assessment/ recruitment?	Family History a) Was the possibility of LFS taken into account?	Family History b) Were family members living outside the country taken into account?	**Overall Assessment**: Likelihood of adequately including persons from minority groups at high risk in the study catchment area
#12: BONN Kuhl [79-81] Schrading [82] Background Meindl [83] Germany 629 women, Prospective, (1996-2006)	Annual MM and dynamic MRI, semi-annual CBE and US ========== 76 BC cases in 68 women: 12 DCIS, 64 invasive: (50 T1, 10 T2, 1 T3, 3 T4) Familial BC often has atypical, benign appearance. Large % of the cancers occur in the posterior breast. *BRCA*1-associated invasive BC had no calcifications, would not be recognized on MM. Conclusions: • Need to tailor surveillance strategies for women with ↑ BC risk to risk category. • MM probably of limited usefulness among *BRCA*-1 mutation carriers. • Due to ↑ vulnerability to ionizing radiation, suggest discontinuing MM among *BRCA*-1 carriers, instead use MRI with or without US for screening. • MM may yield diagnostic information (μcalcifications) to clarify CE seen with MRI in BRCA2 mutation carriers and those at moderate risk.	By the High-Risk clinics of the Department of Gynecology	• Proven *BRCA*1/2 mutation OR Fulfilled criteria for ↑ familial risk by the GCHBOC (See #11, above): • *Moderate risk*: (any of these) -- ≥ 2 relatives with BC or OC, ≥ 1 diagnosed before age 50, or --Relative with BC < age 35, or --Relative with OC ≤ age 40, or --Male relative with BC, or --Relative with bilateral BC OR • *High risk*: (any of these) -- ≥ 2 relatives with BC < age 50, or -- ≥ three 1st or 2nd degree relatives with BC on the same side of the family, or --Women with both BC and OC AND • No current clinical manifestations of BC • No bilateral mastectomy • No diagnosis of metastatic disease • No chemotherapy within last 12 M	In a background article to this study [83], note high prevalence of 5382insC[33] mutations that originated in the Ashkenazi population	Possibly, with respect to the outcome, by performing a comprehensive analysis of *BRCA*1/2 mutation profiles in a background article to this study [83]	No, but allowing inclusion based on single 1st degree relative could have this effect to some extent	Not explicitly	**0.75** • Allowing inclusion based on a single relative makes it more likely that LFS taken into account. • In Ref. [83] note is made of high prevalence of 5382insC[33] mutations that originated in the Ashkenazi population, but no further reference in the study articles themselves • Actual recruitment procedure/how the families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment population, and the minorities therein.
#13 DÜSSELDORF Lux [84, 85] Germany, 761 women, cross-sectional and prospective design (269 women participated in the latter part of the study) (1994-2002 cross-sectional, questionnaire follow-up 1998-1999)	Semi-annual CBE and breast US from age 25, annual MM from age 30 (or 35 depending on breast density) Annual breast MRI if high risk or unclear US ========== 9 breast cancers (by self-report of histopathologic result of suspicious findings) (5 detected by MRI, 1 by MM, 2 by CBE, 1 by US) MRI had highest percentage (28%) of suspicious findings of all methods, but was used the least frequently (altogether 8 benign lesions and 5 unclear, in addition to the 5 malignant findings) Conclusion: "Intensified early cancer detection programmes for women at risk provide a less invasive option than chemoprevention or prophylactic surgery. Although the methods are used at high frequency, it seems feasible to motivate women at risk to participate." (p. 399) [84]	Attended cancer genetic clinic between 1994 -2002	*High risk group*: • ≥ two 1st degree relatives with BC or OC, 1 diagnosed before age 50 or patient herself, or • One female 1st degree relative or patient herself with BC < age 30 or bilateral cancer < age 40 or OC < age 30, or • 1 male relative with BC (N=416 without BC, N=140 with BC or OC) *Not in high risk for hereditary BC or OC:* (N=179 without BC, N=26 with BC or OC)	No	Not explicitly, but inclusion based on a single 1st degree relative could have this effect to some extent	Not explicitly	**0.5** Actual recruitment procedure/how the families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment population, and the minorities therein. Inclusion on the basis of a single relative makes it a bit more likely that LFS taken into account.

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assess-ment?	a) Was the possibility of LFS taken into account?	b) Were family members living outside the country taken into account?	
#14 ITALY MULTI-CENTER Sardanelli [86, 87] Background: Sardanelli [88] Manfrin [89] Santoro [90] 501 women (1592 screening rounds) Prospective (the women were enrolled between 2000- 2007)	2 annual rounds of assessment with: MM, US and CE-MRI and physician-performed CBE, thereafter ≥ 1 y follow-up with CBE; MM + US and optional MRI Average: 3.2 rounds per participant ========== 49 screen-detected BC, 3 interval BC (44 invasive, 8 DCIS, 72% node negative in those explored) Sensitivity: MRI = 91%, MM = 50%, CBE = 18%, US = 52% 49 false positives: MRI had marginally lowest specificity and clearly poorest PPV of all the methods <u>Conclusion:</u> "MRI largely outperformed MM, US, and their combination for screening high-risk women below and over 50" (p. 94) [87]	Persons fulfilling criteria at any of 18 participating centers	• Women ≥ 25 y (except with very early onset in a close relative) AND • *BRCA*1/2 mutation carrier OR • 1st degree relative of *BRCA*1 or *BRCA*2 mutation carrier OR • Strong FHx: 3+ 1st or 2nd degree relatives with any of the following: female BC (<60 y), OC or male BC (self may be included as a case) Excluded: Pregnancy, lactation, current chemotherapy, terminal illness, contraindications to MRI or personal BC if bilateral complete mastectomy	No		Not explicitly, but importance of "clinical judgement" for helping to identify women at high risk was emphasized [87]	Not explicitly	**0.50** • There was explicit recognition of the importance of "clinical judgement" in risk assessment. • Actual recruitment procedure/how the families were detected not sufficiently described to ascertain whether there was systematic surveillance of the population, and the minorities therein. • The only possibility to include those with LFS if 1st degree relative of a known mutation carrier
#15 MODENA Cortesi [91,92] Federico [93] Italy 1325 women, Prospective (1994-2005) Background: Cortesi [94]	• CBE & US (semi-annually fr. 25 y if BRCA+, fr. 30 y if high or intermediate risk) • MM (at varying intervals ∝ age & risk) • MRI (annually for all participants) ========== 44 BC cases (28 infiltrating, 16 DCIS) 5 in BRCA carriers, 23 in high risk group, 11 in intermediate risk group, 5 in slightly ↑ risk group. MRI had highest sensitivity (100%) <u>Conclusion</u>: Rate of cancers detected in women with *BRCA* mutations or strong FHx greater were than expected, justifying the surveillance program. Prospective trials needed for women from families with BC or OC	Collection of FHx through detailed question-naires and interviews, FHx traced at least 4 generations, including paternal side, and as far backward and laterally as possible	• Asymptomatic woman, age 35-65 AND • *BRCA*1/2 mutation carrier (N=48) OR • High risk (N=674) {(≥ 3 relatives diagnosed with BC or OC in 2 different generations with ≥ 1 a 1st degree relative of the other 2 (unless male is interposed) AND ≥ 1 BC diagnosed before 40 y or bilateral) OR ≥1 BC in family before 35 OR ≥ BC + OC in same woman} OR • {Intermediate risk (N=257) 229 had 1st degree, 28 had 2nd degree relatives with BC (lifetime risk of BC estimated at 18-29% according to the Gail model) } OR • Slightly ↑ risk (N=346) 303 had 1st degree, 43 had 2nd degree relatives with BC (lifetime risk of BC estimated at 6-18% according to the Gail mode)	Yes, references cited in the introduction and the discussion of [94] to high risk among Ashkenazi women	Not explicitly	Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS is taken into account	Not explicitly, but detailed questionnaire and interview plus breadth of the history increases likelihood that those outside the country would be included	**0.75** • Recruitment procedure/how families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment area & minorities therein. • Detailed individualized information & allowing various risk levels may have done this, to some extent

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ===== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Minority Groups at High Risk		Family History		**Overall Assessment**: Likelihood of adequately including persons from minority groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If noted, were they taken into account in the actual risk assessment/ recruitment?	a) Was the possibility of limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#16 MILAN Trecate [95] Italy 116 women, Prospective (2000-2005)	Annual CBE, MRI,US, MM ===== 12 BC cases detected (11 detected by MRI, 6 detectable only by MRI, 6 < 1 cm, 1 *in situ*, 10 invasive) (3 false positives with MRI) Conclusion: MRI can detect mammographically occult BC, and is best combined with 2nd look evaluation via US when MRI alone yields a positive result	From breast units with both medical genetics and breast MRI facilities, *BRCA*1/2 testing offered to all	• Carrier of *BRCA*1/2 mutations OR • *BRCA*1/2 mutation in a 1st degree relative OR • Personal history of BC (N=41) or OC (N=12) AND ≥ 50% chance of carrying *BRCA*1/2 mutations OR • > 50% chance of carrying *BRCA*1/2 mutations by FHx: -- ≥ 3 cases of BC before age 60 in 1st or 2nd degree relative OR -- ≥ 3 cases of BC before age 60 and OC at any age OR -- ≥ 3 cases of BC before age 60 and male BC at any age	No		Not explicitly, the only way to facilitate inclusion of those with LFS would be if 1st degree relative of a known mutation carrier	Not explicitly	**0.25** • The only possible way to facilitate inclusion of those with LFS would be if 1st degree relative of a known mutation carrier
#17 SZCZECIN Gronwald [96] Background: Górski [97] Brozek [98] Poland, 414 women, Over age 25 Prospective, minimum 18 month follow-up (49% had BC)	Annual MM from age 35 (81.1% had at least 1 MM) MRI offered free of charge to all mutation carriers, only received by 12 of 212 of the participants without BC (MRI available at only 1 center, Krakow and transportation costs carried by patient) ===== Information given concerning MM and MRI use, as noted above, as part of the survey concerning preventive measures. However, no specific information reported regarding imaging-related outcomes in this cohort.	Residents of Poland counseled at Szczecin Center or affiliated outpatient clinic	• Carrier of 1 of the 3 "Polish" *BRCA*1 founder mutations considered to account for ~ 90% of the total mutation burden AND • Counseled at Szczecin Center or affiliated outpatient clinic. AND • Diagnosis from those seeking genetic counseling made at one of the centers in Poland	Not explicitly, but one of the 3 mutations is 5382insC, which is noted to be one of the founder mutations of the Ashkenazi	Partially by including the 5382insC mutation as one of the 3 that are analyzed	No	Not explicitly	**0.5** • By including the 5382insC mutation in analysis, partial account would have taken for the specific risk among Ashkenazi who participated in the study. However, it is not clear that this was done by design in [96] • Unclear how the participants were recruited. In Ref. [98] a study of 4 BRCA1 mutations in patients with BC, 5382incC and 185del AG were explicitly assessed—note high frequency of 5382incC in the Polish population: obviously done after the main study. • The statement in Ref. [98] (p. 329) "[The] Polish population is not ethnically mixed because of the loss of a considerable number of ethnic groups from Poland's territory" could be interpreted to imply that there is no need to give special attention to minority groups that may be at high risk.
#18 **KRAKOW** Popiela [99] Poland, 379 women with no breast pathology on US or MM	MRI subsequent to MM and US On MRI breast pathology detected in 37 women, 33 underwent open surgical biopsy. 17 benign and 16 BC pathologies visualized only on MRI. MRI sensitivity 93.7%, specificity 64.7% Conclusion: "All women with a 20% or greater lifetime risk of developing BC should undergo annual MRI as a diagnostic adjunct to US and MM." (p. 55)	In collaboration with the International Hereditary Cancer Center of Pomerania Medical University. Queries about all known cases of cancer, family tree constructed for complete FHx Data on DNA testing plus detailed questionnaire plus family interview	≥ 1 relative with BC < 50 y or OC at any age	No		Not explicitly, but allowing inclusion on the basis of a single relative makes it more likely that LFS is taken into account	Not explicitly, but detailed questionnaire and interview plus breadth of the history increases likelihood that those outside the country would be included	**0.75** Actual recruitment procedure/how the families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment population, and the minorities therein. Inclusion on the basis of a single relative makes it a bit more likely that LFS taken into account. Detailed FHx including family tree, questionnaire and interview may increase likelihood of including family members outside the country

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was the possibility of limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#19: MAGNETIC RESONANCE IMAGING STUDY GROUP (STIC IRM 2005) MULTICENTER, FRANCE Brédart [100, 101] France, 1561 women Prospective 1–5 month follow-up (Recruitment period: 2006-2008)	Compared (MRI+MM ± US) and (MM ± US) ========== Evaluated anxiety and specific distress: • 7D pre-imaging surveillance, • 0 – 2 D post- imaging surveillance • 15 to 150 D post-imaging surveillance Conclusion: Surveillance with MRI did not appear to have greater psychological effects than standard imaging alone. Discomfort with MRI in > 20% of the women, due to duration, immobilization, position or noise. Perception of care and experience were more positive with MRI	21 centers in France experienced in breast MRI	No clinical signs of BC, age 20-70, no ongoing cancer tx., no metastases, no bilateral mastectomy AND FOR MRI (lifetime BC risk ≈40% – 60%) • Documented genetic mutation, OR • Non-tested women with ≥ 40% probability of a genetic mutation OR • 1st degree relative with ≥ 80% probability of a genetic mutation FOR MM ± US (lifetime BC risk ≈15% – 20%) • Age 40-50y with Hx of pathological breast lesion or BC OR • Only one 1st degree relative with BC at age 50-70y OR • Contraindication to MRI	Reference cited in the discussion of Ref. [101] to high risk among Jewish women However, in description of actual demographics of the study population, no information on ethnicity or immigrant status	Not explicitly	Not explicitly, but potential lack of knowledge about FHx. was noted	Not explicitly	**0.75** • High risk ethnic group mentioned in publication, though it is unclear whether and if so, how this was actually taken into account in risk assessment and recruitment. • Actual recruitment procedure/how the women at high and moderate risk were detected were not described with respect to whether there was systematic surveillance of the population, and the minorities therein. • Potential lack of knowledge about FHx was noted
#20 INSTITUT CURIE, PARIS Daguet [102] Background: Dorval [103] Eisinger [104, 105] France 85 women, mean age 43 y Prospective, (mean follow-up 2.7 y, 231 examinations) (2000-2006)	Annual MRI, US, MM ========== 8 BC detected (3 *in situ*, 5 invasive) (7 diagnosed by imaging, 1 interval cancer) MRI had the highest sensitivity (95%), but marginally the lowest specificity Conclusion: Clear benefit of MRI seen for this population	Oncogenetic service Universal health care noted to be provided in France [Dorval 2011], such that the costs of cancer genetic consultations, BRCA1/2 testing and subsequent care would be covered by the national health insurance.	• Documented BRCA1/2 or p53 mutation	The ethnic-geographic origin is mentioned as a potential predictive factor [104]	Not explicitly	Not directly, but the maternal and paternal branches are specifically mentioned [104]	Not explicitly	**0.75** • The ethnic-geographic origin is mentioned as a potential predictive factor, though it is unclear whether and if so, how this was actually taken into account in risk assessment and recruitment. • Full coverage by national health insurance would provide a better chance for population coverage. • Actual recruitment procedure/how the women at high risk were detected was not described with respect to whether there was systematic surveillance of the catchment population, and the minorities therein.
#21 NORTHERN FINISTÈRE Lapierre-Combes [106] France 51 women (9 with a history of BC) Retrospective (2003–2007)	MM, US, MRI ========== 9 (18%) invasive BC detected with MRI (all but 1 multifocal or multicentric, 4 recurrent) Positive MRI: 2 of 24 women with high risk 12 of 21 women with radio-clinical discordance Benign pathology in 4 patients Conclusion: Indicates the important role of MRI in diagnostic challenges within invasive breast cancer diagnostics	Series of all patients who fulfilled entry criteria at the Northern Finistère	{(High risk: • 3 cases of BC or OC in the same branch of the family (1st or 2nd degree relative) --OR-- • 2 cases of BC or OC in the same branch of the family (1st or 2nd degree relative) 1 case < 40 y.o., male or 1 OC --OR-- • BRCA1 or BRCA2 carrier or 1st degree relative of a carrier) AND/OR dense breasts AND/OR radio-clinical discordance AND/OR implant } AND normal MM + US	No		Not explicitly	Not explicitly	**0.5** • The entry criteria were broader than only recognized high risk, and so some women who participated in MM screening were included, irrespective of risk.

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was the possibility of limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#22 VIENNA Riedl [107] Background: Kroiss [108, 109] Austria, 327 women, (672 complete imaging rounds) Prospective (1-7 y follow-up) (1999-2006)	Annual MM,MRI, US (the latter semi-annually, if *BRCA*1/2 mutation carrier) ========== 28 BC cases, (11 DCIS) (14 cases detected by MM, 12 by US, 24 by MRI) (MRI had highest sensitivity and detected significantly more DCIS, but lowest PPV of all the modalities. 35% of false positives were ATDH) Improved detection of pre-invasive lesions with MRI, secondary prevention by removing ATDH, as tissue with a high malignant potential Conclusion: MRI improves detection of invasive and pre-invasive cancers in high-risk populations, as well as pre-malignant lesions and should be incorporated into BC surveillance of these women.	Network of 35 cooperative counselling centers for familial BC and OC in Austria	• BRCA1/2 mutation OR • ≥ 3 relatives same side of family with BC < age 61, OR • 1 relative with OC, OR • ≥ 2 relatives, same side of family with BC < 51 y, OR • ≥ 1 relative with BC <36 y, (one of the relatives must be 1st degree or the woman herself) AND • Not currently lactating or pregnant, • No bilateral mastectomy, metastatic disease, or within 1 y of being treated for BC, • No implanted pacemaker (If from a family with proven mutation and not a carrier, also excluded)	Ashkenazi, in a background article to this study [108]	Possibly, for outcome, by performing comprehensive analysis of *BRCA*1/2 mutation profiles in a background article (129), in which 13 % carried Ashkenazi founder mutations (185delAG or 5382insC)	No explicitly, But allowing inclusion on the basis of a single relative makes it more likely that LFS to be included.	Not explicitly	**0.75** • Allowing inclusion based on a single relative makes it more likely that LFS taken into account • In Ref. [108] note high prevalence of 5382insC[33] (Ashkenazi) mutations, but no further reference in the study • Recruitment procedure/ how families were detected not sufficiently described to ascertain whether there was systematic surveillance of the catchment population, and the minorities therein
#23 STOCKHOLM Arver [110, 111] Zelada-Hedman [112] Sweden, 160 families, Retrospective (1997-2000) and 12 month follow-up on the psychological outcomes Background: Arver [113] Brandt [114] Czene [115] Hemminki [116, 117] Margolin [118] Von Wachenfeldt [119]	Annual MM and CBE starting at age 30 for women at high risk Carriers of *BRCA* 1/2 mutations were informed about prophylactic mastectomy and oophorectomy [111] ========== 76 BC cases detected 27 disease-causing *BRCA* 1/2 mutations detected. All BC-only families with a mutation had ≥ 1 case of BC < age 36. With information and support, healthy self-referred women from these high risk families did not show adverse psychological effects of genetic testing at follow-up [111] Conclusion: Decreasing age of onset was observed with successive generations. This should be considered with regard to surveillance options. According to risk calculations, starting surveillance 10 years earlier in women at high risk is considered to be justified [114]	Apparently through the oncogenetic counselling program in Sweden, to which "cancer-prone" families are referred, self-referral permitted. Can also be referred by physician (most frequently primary care physician or gynecologist) In Sweden, oncogenetic counseling is centralized, and is offered at 6 university hospitals [113] BC risk calculations based on FHx and contralateral BC were computed for immigrants only for their time in Sweden [116] The attendees at the clinic have a higher SES than women living in the same area [119]	• ≥ 2 1st or 2nd degree relatives with ≥ 1 case of BC, and ≥1 case of OC, or one person with BC and OC, OR • ≥ 3 1st or 2nd degree relatives with BC, ≥ 1 before age 51, or • Two 1st or 2nd degree relatives with BC, ≥ 1 before age 41, or • One family member with BC before age 36, or • ≥ 2 1st or 2nd degree relatives with OC, or • One family member with OC before age 51 Ref: [110]	Yes, Jewish, Icelandic, Dutch	Only with respect to genetic testing, by performing separate screening for the Ashkenazi (185delAG, 6174delT and 5382insC) and Dutch (3867G→T and 6503delTT) founder mutations on persons who belonged to those groups	Not explicitly, but allowing certain single cases in a family could have this effect to some extent (In the narrative of Ref. [112] note is made that *BRCA*1 mutations are associated with early onset of BC in Jewish women without FHx, though 3+ relatives were required in that article for inclusion as a breast-ovarian cancer family)	No Relying upon the national registry could reduce the likelihood that this occurred. Note is made in Ref. [114] of immigration, but "data on family relationships were obtained from the multi-generation register, where children born in Sweden in 1932 and later are registered with their biological parents as families" [114] Mothers of all women with BC were identified from 1961 to 2004, resulting in 48, 259 mother/daughter pairs in which the daughter had BC. Since 1991 the Multigeneration Register is "considered complete" [115] However, first-generation immigrants were defined as those without identified parents in the data base" [117]	**1.50** • Explicit note made of Jewish, Icelandic & Dutch groups as high risk, separate analysis was performed for founder mutations specific to participants who belonged to those ethnic groups. • Allowing inclusion based upon a single family member makes it more likely that LFS was taken into account. The possibility was noted that women at high risk for *BRCA*1 mutations could have a negative FHx. • Relying upon the national registry would reduce the chances of taking into account family members living outside the country, especially since 1st generation immigrants were defined as "without parents" in the data base [117] • Actual recruitment procedure and how the families were detected were not sufficiently described to ascertain whether there was systematic surveillance of the catchment population However, permitting self-referral and referral from 1° care physicians could allow better coverage of the catchment area. Contrarily, it is found that the attendees have a higher SES than women living in the catchment area. [119]

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was the possibility of limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#24 NORWAY-MULTICENTER (A) Dørum [120] 845 women (754 without previous BC or OC) (1992 – 1997) Prospective	Annual CBE, MM (US and fine needle aspiration when indicated) from age 25 or 10 y before youngest family member was affected ========== 23 cases of BC, all in women age 30 or over, 89% detected before spread Conclusion: In this group of women with familial breast/ovarian cancer, BC screening recommended starting at age 30.	Self-referral or referred by physician for genetic counseling	• 1 case of OC and 1st or 2nd degree relative with OC OR • 1 case of OC and 1st or 2nd degree relative with: BC ≤ 60 OR • 1 case of OC+ BC (≤ 60) OR • OC diagnosis that could not be confirmed histopathologically and any of the above criteria	Reference cited in the introduction of the paper to high risk among Ashkenazi women	Not explicitly	Not explicitly, but by allowing a single family member as a criterion, and by obtaining "complete family history including 1st & 2nd degree relatives", information about LFS was implicitly taken into account, as least to some extent	Not explicitly, but by obtaining a "complete family history including 1st & 2nd degree relatives", implicitly yes	**0.75** • Permitting self-referral or from physician could allow better coverage of the population • While not explicit, by obtaining a "complete family history including 1st & 2nd degree relatives", relatives outside the country are less likely to be excluded • Allowing inclusion based on a single relative makes it more likely that LFS taken into account
#25 NORWAY-MULTICENTER (B) Hagen [121] Background: Albrektsen [122] 491 women Prospective (2002 – 2005)	Annual MM + MRI ± US ========== 25 cases of BC (5 as interval cases). At the time of diagnosis, 19 /22 detected by MRI and 12/24 by MM. 4 DCIS, 21 invasive ductal carcinoma. Conclusion: MRI has greater sensitivity than MM for detecting BC at stage < pT2.	Women found to have a truncating BRCA1 or BRCA2 mutation, as identified at several Norwegian medical genetic centers	• Truncating BRCA1 or BRCA2 mutation • No contraindications to MRI (including severe claustrophobia) • Not breast feeding or pregnant	Reference cited in the introduction to high risk among Ashkenazi women	Not explicitly	No	No	**0.25** • Awareness of high risk ethnic minority groups indicated. • Actual recruitment procedure/how the families were detected not sufficiently described to ascertain whether there was systematic surveillance of the population, and the minorities therein. • Possible reliance upon the national cancer registry [122] could reduce the chances of taking into account family members living outside the country.
#26 BRNO MMCI Foretova [123] Background: Foretova [124] Mateju [125] Czech Republic 284 women (488 examinations) Prospective (2005-2008)	MRI, MM, US (starting at age 25 or earlier if the youngest BC occurred in the family before age 35) ========== 6 BC cases (all N0) (all detected by MRI—MM was negative in all cases, US negative in 2 cases, positive in 4 cases as a secondary exam after MRI	Testing of 3000 patients and 2000 family members at the MMCI Genetic testing performed if: • Sporadic BC or OC before age 40 • Sporadic bilateral BC or OC before age 50 • Sporadic medullary BC or triple negative BC before age 50 • 2 occurrences of BC or OC in the same person at any age • Male BC • Families with 2 cases of BC or OC in close relatives (1 case < 50) • Families with ≥ 3 cases of BC or OC at any age --All testing covered by the National Health Insurance --Note "more frequent referrals from oncologists and other specialists"	BRCA1 or 2 mutations or others at high risk of breast cancers	Yes, the ethnic demography and historical occurrences in the Czech Republic, including the Holocaust explicitly discussed. The substantial influx of other nations in the Czech population explicitly noted [124] Discusses high risk in Iceland, Israel. The mutations from various ethnic groups in Europe are noted.	Possibly, for outcome, by performing comprehensive analysis of *BRCA*1/2 mutation profiles, including mutations from various European ethnic groups, including from Norwegian, Ashkenazi and from other European and non-European groups [123].	Not explicitly, but by allowing a single family member as a criterion, implicitly could be to some extent	Not explicitly	**1.25** • Apparently broad referral system with full coverage by national health insurance would provide a better chance for population coverage • By performing comprehensive analysis of *BRCA*1/2 mutation profiles, found e.g. that 13 % carried Ashkenazi founder mutations • Explicit awareness of ethnic diversity in the country's history, with high risk ethnic groups discussed in publications

Table I. Continued.

Center 1st Author, [Ref. Number] Country, # participants, Design (Years)	Screening methods ========== # detected cases, Benefit of trial	Recruitment of participants	Criteria for entry	Ethnic Minority Groups at High Risk		Family History		**Overall Assessment:** Likelihood of adequately including persons from minority ethnic groups at high risk in the study catchment area
				a) Were they noted? If yes, which?	b) If yes, were they taken into account in risk assessment/ recruitment?	a) Was the possibility of limited family structure taken into account?	b) Were family members living outside the country taken into account?	
#27 DUBLIN Mulsow [126] Ireland 1145 women Prospective (2005 - 2008)	The option of surveillance was offered: Medium risk: CBE + MM annually or biannually High risk: "Intensive surveillance" was one of the options (note that most patients opt for surveillance) ========== 2 BC cases detected (1 presumably at CBE, the other at prophylactic mastectomy) Emphasize the need to enable patients to make "informed choices regarding their follow-up and management" (p. 33)	Patients referred to a family BC risk assessment clinic (46% from the clinic itself, 30% directly from primary care, 10% from family members attending the clinic and 14% from elsewhere, including private clinics, gynecology and oncology services)	Medium risk (NICE guidelines): • 1 1st degree relative with BC < 40 OR • 2 1st or 2nd degree relatives with BC average age >50 OR • 3 1st or 2nd degree relatives with BC average age >60 High risk (NICE guidelines): • 2 1st or 2nd degree relatives with BC < 50 OR • 3 1st or 2nd degree relatives with BC < 60 OR • 4 relatives with BC OR • BC gene identified in a family member OR • 2 1st or 2nd degree relatives with BC or OC plus: --BC < 40 --OC < 50 --BC + OC in same woman --Ashkenazi Jewish ancestry --BC in a male relative --1st or 2nd degree relative with sarcoma < 45	Yes, Ashkenazi Jewish	Yes, as a subsidiary risk factor, under quite stringent conditions	Not explicitly, but by allowing a single family member and by including Ashkenazi Jewish as a criterion, and by the use of a "detailed family history questionnaire" whereby missing family members could be noted, this could have been achieved, at least to some extent.	Though not explicitly mentioned, the use of a "detailed family history questionnaire" and that family history was verified by the woman herself, makes this more likely.	**1.5** • Broad referral system, including primary care would provide a better chance for population coverage, including a substantial proportion of young women in their teens and 20s—who would not otherwise be under any surveillance • Ashkenazi Jewish ethnicity included as a subsidiary risk factor, but under quite stringent conditions. • By confirming family history with the woman herself and the use of a "detailed family history questionnaire" LFS & family members living outside the country are more likely to have been taken into consideration.

Coding for Overall Assessment: 3, Active surveillance with a very high participation rate of the entire at-risk minority population in the catchment area; adequate account taken of eventual limited family structure and family living outside the country. 2, Systematic efforts were made to include at-risk minority populations, but unlikely to have achieved sufficiently high coverage to do so. 1, Although not taken into account for recruitment, high risk ethnicity and/or limited family structure and/or family members living outside the country was considered in the study design. 0, No attention whatsoever to high risk ethnicity nor to limited family structure nor to family members living outside the country. Recruitment procedure and entry criteria render it very unlikely that women at high breast cancer risk who are from ethnic minority groups were included in the program. ATDH, atypical ductal hyperplasia; BC, breast cancer; CBE, clinical breast examination; CE, contrast enhanced; D, day(s); DCIS, ductal carcinoma *in situ*; FHx, family history; GCHBOC, German Consortium for Hereditary Breast & Ovarian Cancer; GP, general practitioner; Hx, history; LCIS, lobular *in situ* carcinoma; LFS, limited family structure; M, month(s); MARIBS, magnetic resonance imaging for breast cancer screening; MM, mammography; MMCI, Masaryk Memorial Cancer Institute; MRI, magnetic resonance imaging; MRISC, Multicenter Dutch MRI Screening Study; OC, ovarian cancer; PIMMS, psychological impact of mammography screening in women with family history of breast cancer; PPV, positive predictive value; RRSO, risk-reducing salpinghooophorectomy; RT, radiation therapy; SES, socioeconomic status; sig, statistically significant; STIC IRM, Magnetic Resonance Imaging Study Group France; UMC, university medical center; y, year(s).

The Stockholm Center (#23) (110-112) reported on 160 families receiving annual mammography and CBE. The two Norwegian Multicenter Studies (##24 and 25) (120,121) followed 754 and 491 women at high breast cancer risk for 5 and 3 years, respectively. In Study Center #24 (120) CBE, mammography and in some cases ultrasound were used, and in #25 (121) mammography, MRI and in some cases ultrasound.

In the Czech (Brno) Study Center (#26) (123) MRI, mammography and ultrasound were provided to 284 women at high risk, with follow-up reported for 3 years. The Irish (Dublin) Study Center (#27) (126) reported the results of 3-year follow-up of 1145 women at medium and high breast cancer risk with the option offered of imaging surveillance using CBE and mammography.

5. Benefits of imaging surveillance for women at high breast cancer risk as assessed in the 27 study centers

In all the centers where it was applied, MRI was recommended for screening women at increased risk, since it showed the highest sensitivity and thereby provided early breast cancer detection, frequently while still carcinoma *in situ*. However, MRI also yielded many false positive results, often more than mammography. This low positive predictive value of MRI was of concern and other modalities (mammography and/or ultrasound) were also usually recommended. On the other hand, the Bonn Center (#12) (79-82) found that MRI alone was sufficient among women with *BRCA*1 mutations. These authors reported that mammography did not provide additional information for early breast cancer detection in this group. Considering the heightened vulnerability to ionizing radiation among *BRCA*1 mutation carriers, these authors recommended that mammography be discontinued for this group. Similarly, in the Dutch Multicenter Study (#1) (37-46) MRI appeared to be effective for *BRCA* mutation carriers and was generally more sensitive than mammography. However, it was also noted that mammography detected some early cancers missed by MRI. Overall, the use of MRI and more intensive screening starting at a younger age provided earlier detection, such that there was a clear benefit for women with increased breast cancer risk.

From the Stockholm Study Center (#23) (110-112) which focused on high-risk families, the decreasing age of cancer onset with successive generations was viewed as important for choosing surveillance modalities (110,114). The investigators from the Dusseldorf Center (#13) (84,85) stated that intensified early cancer detection programs for women at risk provide a less invasive option than chemoprevention or prophylactic surgery. Notwithstanding the high frequency of surveillance, these authors found it feasible to motivate at-risk women to participate. Despite the problems surrounding false positive findings, MRI was found to be acceptable by these women (84,85). This latter conclusion was shared by authors from the Dutch Multicenter study (#1) (38).

6. Recruitment of women into the programs and considerations of ethnicity and high risk, including testing for relevant gene mutations

Most of the study participants were recruited from specialized clinics for women at high risk. It was noted that self-referral or referral from primary care physicians was possible for some of these programs. The latter include: UK Study Centers (#4 and #8) MARIBS (52-67) and psychological impact of mammography screening in women with family history of breast cancer (PIMMS) (73,74), the Stockholm Study Center (#23) (110-112), one of the Norwegian Multicenter Studies (#24) (120), the Dublin Study Center (#27) (126) and possibly the Czech (Brno) Study Center (#26) (123). The explicit possibility of self-referral or referral from primary care physicians might improve the coverage of the catchment area and thereby might have increased the chances of including a broader sampling of women at high breast cancer risk.

Ethnicity, including ethnic minority groups at increased breast cancer risk was mentioned in some of the studies as part of their introduction or general discussion. In a study (47) which provided relevant background for the Dutch Multicenter MRI Screening Study, MRISC (#1), a substantial percentage of women from minority ethnic backgrounds, including those with parents born elsewhere, were noted to have been referred to genetic counseling centers in the Netherlands. On the other hand, in the MRISC-B Study, requiring Dutch language proficiency (37) may have excluded a substantial percentage of ethnic minority women. Women from non-white minority ethnic backgrounds appear to have been under-represented in the UK MARIBS Study (#4) comprising only 2.3% of the sample according to the reported data (62). The statement in Brozek *et al* (98): '(The) Polish population is not ethnically mixed because of the loss of a considerable number of ethnic groups from Poland's territory' (p. 329) could be interpreted to imply that for the Polish Szczecin Study (#17) no special attention was given to minority groups that may be at high risk. In contrast, explicit appreciation of the country's ethnic diversity was indicated in a background article by the first author of the Czech Brno Study (#26) (124).

For a few centers [Szczecin #17 (96), Stockholm #23 (110) and Brno #26 (123)] relevant gene mutations were tested for some ethnic groups at high risk. It might be inferred from some studies (79,83,107) that the Bonn and Vienna Centers (##12 and 22) also tested for these gene mutations. In the Nightingale and PIMMS Studies from the UK (##4 and 8) (73,74) ande in the Dublin Study (#27) (126) high risk ethnicity (Ashkenazi Jewish) was considered as a subsidiary factor under stringent conditions, i.e. that two relatives with breast or ovarian cancer had already been identified.

7. Family history assessment, including reliance on national data registries

Several of the study centers allowed a woman to be included in their program if she had a single family member with breast cancer or ovarian cancer diagnosed at a young age. This might partially have taken limited family structure into account. However, limited family structure per se (24) was not examined in any of the studies.

Family members outside the country were not explicitly taken into account in any of the studies. Some of the Centers, for example, the German Multicenter Study (#11) (78), the Italian Modena Study (#15) (91-93), the UK Study (#10) (77) of young women with increased risk and the Polish Krakow Study

(#18) (99) described a very detailed procedure for taking a family history, and this may have facilitated inclusion of family who lived abroad. An adjudicating panel assessed the family history in the UK MARIBS study (#4) and it might be assumed that this would ensure completeness of the family history data. On the other hand, the adjudicating panel could have introduced greater stringency, as assessed in the sub-study by Evans *et al* (55). In one of the most recent studies from the MARIBS and subsequent Nightingale Studies (#4), it was explicitly recognized that there is a need for 'systematic assessment of family history in primary care or through population-based screening [to] identify appreciable numbers of women in their forties, eligible for additional surveillance' (56) (p. 993).

The Stockholm Center (#23) (110,114) and possibly the Multicenter Norwegian Study (#24) (121,122) relied on National Data Registries for identifying high risk families. Whereas this procedure would facilitate inclusion of at-risk family members living within the country, the likelihood is greater of missing family members outside the country. Moreover, first generation immigrants were defined a priori as 'without parents' in the Swedish database (117), rendering it even more difficult for first generation immigrant women to be included in the high risk programs.

8. Overall assessment of the likelihood of including women at high breast cancer risk and who belong to minority ethnic groups into the 27 study centers

Based on the above considerations, the overall assessment scores were low vis-à-vis the likelihood of adequately including women at high breast cancer risk, who belong to minority ethnic groups and who were residing in the study catchment area. Namely, the mean score was 0.72 [standard deviation = 0.31 (range 0.25-1.5)] from a possible range of 0-3. All but four of the study centers (UK Multicentre #4, Stockholm #23, Brno #26 and Dublin #27) had an overall assessment score <1 and, as indicated, none of the centers had a score >1.5.

9. Broader considerations for Europe based on the present analysis

The present analysis, based on a larger number of European centers and extended for several more years, confirms our previous findings (34) that for women at high risk of breast cancer, intensive screening programs, starting at a younger age and including magnetic resonance imaging were beneficial. The present review on the basis of this extended analysis also confirms our previous conclusion (34) that none of the European study centers made systematic efforts to include women from ethnic minority groups and who were at high breast cancer risk. High-risk ethnicity was not taken into account in recruitment of participants in most of the examined high-risk surveillance studies in Europe. The three exceptions (Nightingale Study #4) (57), (PIMMS, Study #8) (73,74) and (Dublin, Study #27) (126), as noted, considered high-risk ethnicity (Ashkenazi Jewish) as a subsidiary factor under stringent conditions, i.e. that two relatives with breast or ovarian cancer had already been identified. While a few of the examined study centers (96,110,123) did test for the relevant gene mutations of ethnic minority groups at high risk, none of the studies reported active outreach efforts to ensure that these women participated in their programs.

Limited family structure (24) was not adequately considered in any of the reviewed study centers. It has been suggested that the probability models of breast cancer risk need to be revised so that limited family structure is taken into sufficient account. Limited family structure becomes especially problematic when there is a single case of breast cancer in the family. It is here, most notably that these models fail to identify high risk (25). When the family risk for disease is exceedingly high, these missing family links can become critical (16). For ethnic minority groups living in Europe, who have been exposed to war during which many family members have perished, these considerations regarding limited family structure warrant particular attention. For example, cases have been reported for which limited family history due to the Holocaust rendered timely detection of high risk for breast cancer very difficult (127).

Besides the possibility of limited family history, immigrants, refugees and ethnic minority groups, in general, are often geographically dispersed. Information about cancer occurrence may, therefore, be more difficult to obtain and confirm if the medical records are outside the country. We noted this to be particularly problematic for the study centers requiring documentation of all family cases and for those relying on the National Data Registries. None of the study centers explicitly indicated that efforts had been made to ascertain whether there was cancer incidence among family members outside the country.

In the attempt to obtain accurate information about family cancer history, the cultural as well as historical context should also be considered. Grief, fear and denial can hinder reporting the entire extent of family risk (128,129). Insofar as the family has endured trauma, these considerations may become even more salient and protracted. For example, it has been noted that the offspring of Holocaust survivors (second generation) are very susceptible to psychological distress, such that when confronted with breast cancer, they react with extremely high levels of distress (130). This effect appears to be synergistic, such that women with breast cancer and whose parents were Holocaust survivors (Holocaust survivors were defined as those who had been in a concentration camp, forced labor camp or extermination camp in Europe during World War II) had much higher psychological distress than expected, based on the distress levels found for each of these factors alone (131,132). Direct exposure to the Holocaust is also associated with increased risk of breast cancer and other malignancies (133). Other traumatic situations, especially those related to war and upheavals that are still occurring in various parts of the world may well have a similar effect on persons from the affected immigrant and refugee groups (130).

In Europe, disclosure of ethnicity per se may be problematic. Subsequent to World War II, a number of European countries avoided ethnic identification of individuals. It is also plausible that individuals can be reluctant to admit that their origin is other than that of the European country in which they are currently residing. This reluctance, while fully understandable, introduces yet more complexity regarding this topic within Europe. As counter-examples, in countries such as the Canada, USA and Australia, comprised of diverse

immigrant populations since their establishment, asking about ethnicity in the relevant medical setting is not only acceptable, but is considered indispensable for providing adequate clinical care. In these countries, ethnic disclosure has been essential for ensuring appropriate attention to under-represented groups for clinical trials within oncology and elsewhere in medicine (134-136). Moreover, it is well-appreciated that special, often labor-intensive outreach efforts to underserved ethnic minority groups are needed, with attention to structural and attitudinal barriers to cancer screening (33,34,134,137-141). With specific regard to high breast cancer risk, it has been emphasized that 'identification of the ethnic group of families undergoing genetic counseling enables the geneticist and oncologist to make more specific choices…to simplify the clinical approach to genetic testing carried out on members of high-risk families' (p. vi93) (19).

Successful outreach to underserved ethnic minorities requires cultural competence, which includes both knowledge as well as sensitivity (33,34,142-146). Culturally-tailored interventions have been very effective in increasing adherence to breast cancer screening guidelines among under-screened ethnic groups (147-150). As mentioned, women with a foreign birthplace and, especially, recent immigrants appear to be vulnerable for non-attendance in these screening programs (28-35). A poignant example is provided in a study (151) about Russian immigrants to Israel, whose preoccupation was with immediate survival needs, such that attitudes towards breast cancer screening were expressed as: 'I have no time for potential troubles' (p. 153).

This statement reflects another important concern regarding imaging surveillance of women with elevated risk of breast cancer, namely, the substantial possibility of obtaining false positive results from existing screening methods, including MRI. Indeed, in a multi-center study from the USA, Canada and Argentina, among women with increased breast cancer risk and who were eligible to undergo breast MRI, just over half agreed to do so (152). Claustrophobia was the most commonly noted reason for refusal, which may be related to general anxiety about the procedure and its possible results. Concern about additional biopsies or testing was explicitly cited by many women who declined to undergo MRI. It is plausible that this high refusal rate reflects a lack of confidence in the diagnostic accuracy of MRI. Although MRI is reported to be particularly sensitive for women with high breast cancer risk (153), the large number of false positive findings may have a deleterious effect upon quality of life (154). Thus, in the French Multicenter Study #17, although women at high breast cancer risk who underwent MRI had less anxiety at baseline than women at lower risk who were not offered MRI, abnormal surveillance study results were associated with significantly increased anxiety (100). The possibilities for improving the specificity of MRI through e.g. magnetic resonance spectroscopy and diffusion-weighted imaging warrant attention in this context (155-161).

10. Limitations and challenges of this review

Together with our previous study (34), these are the first reviews, to the best of our knowledge, in which the special screening needs of ethnic minority women in Europe at high risk for breast cancer have been examined. Our search strategies were carefully conceived aiming for completeness. The scoring system was heuristic, because of the uncharted nature of this area of investigation. Nevertheless, we consider this scoring system to have good face validity. For some of the centers, inference was needed since the provided information was limited about recruitment of participants. We strove to avoid subjectivity in these ratings via two or more independent assessments.

Admittedly, the formal concept of limited family structure (24) is relatively new. Therefore, it might not be reasonable to expect this consideration to be fully incorporated into the study methodology of the examined centers. Nevertheless, the importance of family truncation as well as dispersion of family members outside the host country should certainly be a routine consideration to achieve adequate risk assessment. Simply stated, a complete family history should be taken 'without borders'.

Another limitation of the present review is that the percentage of ethnic minority women varies greatly across the various European countries, and this was not taken into account in our assessment. Different regions, even within the same country, may have very different proportions of persons who are not of the primary nationality of the country (i.e. immigrants, refugees as well as ethnic minorities having lived in the region for a long period of time). Nevertheless, the needs of such persons, whatever their prevalence in the population, still warrant attention.

A number of questions are raised by the present review. Firstly, in Europe we do not know the preferences of women with an ethnic minority background and who are at high breast cancer risk with regard to approaches to screening. Attitudes regarding disclosure of ethnic identity are also not known. Within this context, issues regarding the safety and security of disclosing one's ethnicity must be clearly addressed and guaranteed. It is known that trauma survivors and their immediate descendants can become extremely distressed when faced with breast cancer. However, it is not known how the generational experience of the severe trauma affects screening behavior among women at high breast cancer risk who are from ethnic minorities. Hence, the most effective cultural-specific strategies to enhance adherence to screening guidelines among these groups in Europe remain to be identified.

11. Suggested next steps

Population-based invitational breast cancer screening programs that already exist in many European countries would be an appropriate starting point for launching this initiative. These programs have a well-documented success in achieving high participation rates and lowering mortality from breast cancer (162-167). Outreach, including the use of multi-lingual media, is increasingly appreciated as an effective strategy for enhancing participation in breast cancer screening programs among ethnic minority groups. Inclusion of trusted community leaders may be particularly helpful (150,168). This type of initiative is currently on-going, e.g. in Stockholm (169).

Several population-based invitational breast cancer screening programs operate in countries whose native populations are at increased risk of carrying deleterious breast cancer

gene mutations. Analysis of cases of interval breast cancers from population-based screening programs underscores the importance of identifying women at high risk e.g. carriers of a more aggressive molecular phenotype such as *BRCA*1/2 mutations (170). Screening at the population level for hereditary and familial cancer syndromes has been demonstrated to be a potentially viable strategy within the European setting (171). Population-based screening programs that tailor to risk profiles also represent a promising possibility, based on a recent study from Italy (172). Especially within such settings, systematic outreach to women at high risk from various ethnic groups would certainly be feasible.

As noted, several European countries have population-based breast cancer screening programs. Unfortunately, however, even more European countries do not (35,173). We would contend that efforts could be particularly promising insofar as they were coordinated with improved and more systematic breast cancer screening programs across Europe.

12. Conclusions

Women from ethnic minority groups in Europe and who are at high breast cancer risk do not appear to have sufficiently benefitted from existing high-risk screening programs. Systematic outreach targeting these populations, in a culturally sensitive manner, is needed. These efforts are likely to be most effective on a European-wide basis. Given the ever-increasing mobility of the global working force and socio-economic migration across national borders, the question of providing adequate breast cancer risk assessment for women of different ethnic origin is becoming more and more relevant. Furthermore, these efforts are in line with the European Union Council's initiative aimed at 'Reducing the Burden of Cancer in Europe' (174).

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