CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

No evidence of excessive cancer screening in female noncarriers from *BRCA1/2* mutation–positive families

S. Guedaoura PhD,[*†] S. Pelletier MPs,[†] W.D. Foulkes MD PhD,[‡§] P. Hamet MD PhD,[||#] J. Simard PhD,[†**] N. Wong MSc,[§] Z. El Haffaf MD,[||**] J. Chiquette MD,[†**††] and M. Dorval PhD[*† ††]

ABSTRACT

Background In families with a proven *BRCA1/2* mutation, women not carrying the familial mutation should follow the cancer screening recommendations applying to women in the general population. In the present study, we evaluated the cancer screening practices of unaffected noncarriers from families with a proven *BRCA* mutation, and we assessed the role of family history in their screening practices.

Methods Self-report data were provided retrospectively by 220 unaffected female noncarriers for periods of up to 10 years (mean: 4.3 years) since disclosure of their *BRCA1/2* genetic test result. A ratio for the annual frequency of breast and ovarian cancer screening exams (mammography, breast ultrasonography, breast magnetic resonance imaging, transvaginal or pelvic ultrasound, cancer antigen 125 testing) was calculated as number of screening exams divided by the number of years in the individual observation period.

Results The annual average for mammography exams was 0.15, 0.4, 0.56, and 0.71 in women 30–39, 40–49, 50–59, and 60–69 years of age respectively. The uptake of other breast and ovarian cancer screening exams was very low. Mammography and breast ultrasonography and magnetic resonance imaging were generally more frequent among participants with at least 1 first-degree relative affected by breast cancer.

Conclusions In most noncarriers, screening practices are consistent with the guidelines concerning women in the general population. When noncarriers adopt screening behaviours that are different from those that would be expected for average-risk women, those behaviours are influenced by their familial cancer history.

Impact Decision tools might help female noncarriers to be involved in their follow-up in accordance with their genetic status and their family history, while taking into account the benefits and disadvantages of cancer screening.

Key Words *BRCA* genes, true noncarriers, cancer screening practices, familial cancer history, cohort studies

Curr Oncol. **2017 Dec;24(6):352-359** **www.current-oncology.com**

INTRODUCTION

In families with a proven *BRCA1/2* mutation, most women who do not carry the familial mutation ("true negatives") can be reassured that they are no longer considered at high risk for breast and ovarian cancer[1–5]. For that reason, such women should be encouraged to adopt the cancer screening practices recommended for women of their age in the general population[1–5]. In Canada, each province operates an organized breast screening program with its own guidelines[6]. At the time of the present study, the Quebec Breast Cancer Screening Program recommended that women 50–69 years of age undergo breast screening mammography every 2 years[7].

Nevertheless, some controversy still surrounds the magnitude of the residual cancer risk in noncarriers based on risk factors other than *BRCA1* and *BRCA2* mutations—especially a significant familial cancer history, which is considered to be among the most important risk factors for breast and ovarian cancer[8–12]. Some studies have postulated a higher risk for noncarriers than for similarly-aged women in the general population. A modest

Correspondence to: Michel Dorval, Centre de recherche du CHU de Québec–Université Laval, Hôpital du Saint-Sacrement, 1050, chemin Sainte-Foy, Québec (Québec) G1S 4L8.
E-mail: Michel.Dorval@crchudequebec.ulaval.ca ■ **DOI:** https://doi.org/10.3747/co.24.3759

elevation, doubling the risk, in true-negative family members in *BRCA*-positive families cannot be excluded[2,4,13]. Being neither massive nor trivial, such an elevation can be cause for caution with respect to the optimistic claim that noncarriers sustain no clinically relevant excess risk burden. Some authors have therefore suggested that noncarriers from *BRCA*-positive families should consider continued screening[14–19].

Information about cancer screening practices among noncarriers from *BRCA1/2* mutation-positive families is limited and inconsistent; whether those women follow general population guidelines for cancer screening is still uncertain. Recent studies reported that some noncarriers "overuse" breast and ovarian cancer screening after genetic testing[20–24]; others reported fewer screening practices[25–27]. Familial cancer history has been suggested as a major factor that could influence use of cancer screening in this population[21–24], but to our knowledge, no study has yet evaluated that hypothesis in real-world conditions. The objectives of the present study were therefore twofold:

- Describe the breast and ovarian cancer screening practices of noncarriers from *BRCA1/2* mutation-positive families.
- Assess the role of family history in the cancer screening practices of noncarriers from *BRCA1/2* mutation-positive families.

METHODS

Participants

Participants were recruited from four cancer genetics clinics in the province of Quebec, in Montreal ($n = 3$) and Quebec City ($n = 1$). Eligible participants were female noncarriers from *BRCA1/2* mutation-positive families tested in the clinics who received their genetic test result between 1 January 2002 and 31 December 2011, and who had not to that point been affected by breast or ovarian cancer. Women who were more than 75 years of age at recruitment or more than 70 years of age at disclosure of their test result were ineligible. The study was approved by the institutional ethics review boards of the participating institutions, and all participants signed an informed consent form.

Data Collection

In this cross-sectional study, participants were asked to report their yearly uptake of all screening examinations for breast cancer [mammography, breast ultrasonography, breast magnetic resonance imaging (MRI)] and ovarian cancer [pelvic or transvaginal ultrasonography, test for serum cancer antigen 125 (CA125)] from the disclosure of their *BRCA1/2* test result to 31 December 2012. The period for which participants reported data was therefore different for each individual. That period was called the "individual observation period." The data for that period were retrospectively collected using a self-administered questionnaire ("screening history diary") developed specifically for the study.

Based on the event history calendar approach[28], the diary included a timeline grid into which participants were encouraged to write significant personal life events that occurred during their individual observation period and that they could later use as cues to help them recall their breast and ovarian examinations. The participants received a suggestion that they use the timeline as a reference when recording, on similarly designed grids (one for each type of examination), the breast and ovarian examinations that they received during their individual observation period. Precise instructions and separate sections were provided to favour the most accurate possible distinction between screening exams and exams scheduled for diagnosis purposes. The diary was extensively pretested before use in the study. Telephone support from research personnel was available for participants needing help to complete the questionnaire.

Familial cancer history was collected about breast and ovarian cancers in first- and second-degree relatives, on both the maternal and the paternal sides. Cancer risk perception was separately assessed for breast and ovarian cancers using one item ("How would you rate your chance of developing breast [ovarian] cancer?") rated on a 5-point scale ranging from 1 ("very low") to 5 ("very high")[29]. The response options "very low," "moderately low," and "neither high nor low" were grouped and designated as "low–moderate cancer-risk perception"; "moderately high" and "very high" were grouped and designated as "high cancer-risk perception."

Analyses

The breast and ovarian cancer screening practices since genetic testing are described on an annual basis, by age stratum (<30 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years). The annual screening frequency for each screening examination was calculated as a ratio: number of screening exams divided by the number of years in the individual observation period. For example, a participant who had 3 mammography exams during a 6-year observation period would have a ratio of 0.5—that is, an average of 1 mammography exam every 2 years. A ratio of 0.67 would represent an average of 2 mammography exams over a period of 3 years. Undergoing mammography at less than 40 years of age or more than once every 2 years, and any use of breast ultrasonography, MRI, transvaginal ultrasonography, or CA125 testing were defined as an "excessive" screening practice compared with the Canadian cancer screening recommendations for women in the general population[30,31].

Associations of cancer screening practices with the variables of interest were analyzed using univariate (chi-square or Fisher exact test) and multivariate models (binary or polytomous logistic regression), overall and by age stratum. Odds ratios (ORs) with their 95% confidence intervals (CIs) were used to report the associations. Explicative variables considered included family history of breast and ovarian cancer in first-degree relatives (≥1 vs. 0), education level (with vs. without college degree), follow-up by a family doctor or a gynecologist (yes vs. no), mutation status (*BRCA1* vs. *BRCA2*), and cancer risk perception (high vs. low–moderate). Two potentially confounding and modifying variables were also considered in the multivariate models: length of the individual observation period (1–2 years, 3–4 years, or ≥5 years), and the cancer

genetics clinic at which the participant was tested (Centre hospitalier universitaire de Québec, Hôpital du Saint-Sacrement; Centre hospitalier de l'université de Montréal, Hôtel-Dieu de Montréal; Sir Mortimer B. Davis Jewish General Hospital; McGill University Health Centre, Montreal General Hospital). The potential confounding effects of those variables were assessed by comparing the crude and adjusted models. In the study, the proportion of missing values was less than 10% for all explicative variables considered in the models. To take into account the potential effect of missing values, sensitivity analyses were performed with and without the missing values; the results were not materially affected. The results reported here are based on a pairwise deletion approach for treating missing values. All significance levels are two-sided (p = 0.05). Statistical analyses were performed using the SAS software application (version 9.4: SAS Institute, Cary, NC, U.S.A.).

RESULTS

Of the 347 eligible women identified, 286 agreed to participate (82%), of whom 220 (63%) completed and returned their questionnaire (Table I). Two thirds of participants had at least 2 first- or second-degree relatives affected by breast cancer, and almost half had a familial ovarian cancer history. Few (n = 17) had a familial history of ovarian cancer only. The participants belonged to families with *BRCA1* or *BRCA2* familial mutations in similar proportions.

Half the participants retrospectively provided information for a period of 5 years or more. Most received regular follow-up, either by a family doctor (91%) or a gynecologist (46%); 42% were followed by both. Only 4% of the women (n = 9) were not followed by any physician. Most participants (84%) reported that their doctors were aware of their genetic status. More than three quarters of the women perceived their breast cancer risk (79%) and ovarian cancer risk (76%) as low–moderate.

Overall, 65% of participants had undergone at least 1 screening mammography exam since receiving their genetic test result (Table II). Slightly more than one third of the participants had undergone more than 1 mammography exam every 2 years. Mammography use started from about the age of 30 and increased progressively by participant age (Table II). On average, respondents 50 years of age and older had undergone a mammography exam slightly more often than once every 2 years, with more than a quarter of that subpopulation undergoing mammography annually. However, 11% of participants in that age group had not undergone mammography since disclosure of their genetic screening test result. In women 40–49 years of age, 21% had undergone mammography once annually. One quarter of women 30–39 years of age had undergone mammography at least once since their genetic testing, and 10% had undergone mammography once annually.

The uptake of the other breast and ovarian cancer screening exams was very low. With respect to breast cancer screening exams, participants 40–49 years of age were the ones who most frequently attended breast ultrasonography exams (19%); those 30–39 years of age were the ones who most frequently attended breast MRI exams (12%). With respect to ovarian cancer screening, little variation in

TABLE I Selected characteristics of the study participants

Characteristic	Value
Patients (n)	220
Mean age (years)	44.9±12.2
Age group at disclosure [n (%)]	
<30 Years	28 (13)
30–39 Years	46 (21)
40–49 Years	57 (26)
50–59 Years	58 (26)
60–69 Years	31 (14)
Education [n (%)]	
Without university degree	108 (49)
With university degree	112 (51)
Genetics clinic [n (%)]	
CHU de Québec, Hôpital du Saint-Sacrement	36 (16)
CHUM, Hôtel-Dieu de Montréal	71 (32)
Sir Mortimer B. Davis Jewish General Hospital	72 (33)
MUHC, Montreal General Hospital	41 (19)
Breast cancer history [n (%)]	
First-degree relatives	
0	88 (40)
1	74 (34)
≥2	58 (26)
First- or second-degree relatives	
0	28 (13)
1	46 (21)
≥2	146 (66)
Ovarian cancer history [n (%)]	
First-degree relatives	
0	167 (76)
≥1	53 (24)
First- or second-degree relatives	
0	121 (55)
≥1	99 (45)
BRCA mutations status[a] [n (%)]	
BRCA1	114 (52)
BRCA2	106 (48)
Individual observation period	
Duration group [n (%)]	
1–2 Years	60 (27)
3–4 Years	52 (24)
≥5 Years	108 (49)
Mean duration (years)	4.9±2.7

[a] Two participants from families positive for *BRCA1* and *BRCA2* mutations.

CHU(M) = Centre hospitalier de l'Université (de Montréal); MUHC = McGill University Health Centre.

TABLE II Cancer screening practices of study participants by age group

Screening practice and frequency	Age group					
	18–29 Years (*n*=28)	30–39 Years (*n*=58)	40–49 Years (*n*=78)	50–59 Years (*n*=84)	60–69 Years (*n*=51)	Overall (*n*=220)
Mean study length per woman (years)	3.3±2.1	3.5±1.9	3.9±2.2	3.9±2.2	3.9±2.1	4.9±2.7
Breast cancer screening						
Mammography frequency [*n* (%)]						
Never	28 (100)	43 (74.1)	30 (38.5)	14 (16.7)	1 (2)	76 (34.5)
Less than once every 2 years	0 (0)	6 (10.3)	16 (20.5)	14 (16.7)	7 (13.7)	41 (18.6)
Once every 2 years	0 (0)	2 (3.5)	8 (10.3)	17 (20.2)	10 (19.6)	29 (13.2)
More than once every 2 years	0 (0)	1 (1.7)	8 (10.3)	16 (19.1)	15 (29.4)	41 (18.6)
Annual	0 (0)	6 (10.3)	16 (20.5)	23 (27.4)	18 (35.3)	33 (15)
Average annual exams	0±0	0.15±0.32	0.4±0.39	0.56±0.35	0.71±0.26	0.41±0.37
Breast ultrasonography [*n* (%)]						
Never	26 (92.9)	51 (87.9)	63 (80.8)	74 (88.1)	48 (94.1)	186 (84.5)
At least once during observation period	2 (7.1)	7 (12.1)	15 (19.2)	10 (11.9)	3 (5.9)	34 (15.5)
Average annual exams	0.03±0.13	0.05±0.15	0.09±0.22	0.06±0.2	0.04±0.2	0.07±0.19
Breast magnetic resonance imaging [*n* (%)]						
Never	27 (96.4)	51 (87.9)	75 (96.2)	77 (91.7)	49 (96.1)	202 (91.8)
At least once during observation period	1 (3.6)	7 (12.1)	3 (3.8)	7 (8.3)	2 (3.9)	18 (8.2)
Average annual exams	0.02±0.13	0.06±0.19	0.01±0.07	0.05±0.18	0.04±0.2	0.04±0.17
Ovarian cancer screening						
Pelvic or transvaginal ultrasonography [*n* (%)]						
Never	27 (96.4)	52 (89.7)	68 (87.2)	71 (84.5)	42 (82.4)	184 (83.6)
At least once during observation period	1 (3.6)	6 (10.3)	10 (12.8)	13 (15.5)	9 (17.6)	36 (16.4)
Average annual exams	0.01±0.06	0.04±0.15	0.09±0.27	0.08±0.22	0.07±0.19	0.07±0.2
Cancer antigen 125 [*n* (%)]						
Never	28 (100)	57 (98.3)	68 (87.2)	74 (88.1)	44 (86.3)	198 (90)
At least once during observation period	0 (0)	1 (1.7)	10 (12.8)	10 (11.9)	7 (13.7)	22 (10)
Average annual exams	0±0	0.02±0.13	0.07±0.23	0.08±0.25	0.07±0.2	0.06±0.2

uptake was observed from about the age of 30 for pelvic or transvaginal ultrasonography and from about the age of 40 for CA125 testing. Younger participants underwent very few screening exams.

The use of mammography, breast ultrasonography, and MRI was generally more frequent among respondents with at least 1 first-degree relative affected by breast cancer than among those without such a relative (Table III). The use of pelvic or transvaginal ultrasonography and CA125 testing was also more frequent among women who had at least 1 first-degree relative affected by ovarian cancer than among those without such a relative.

In participants 40–49 years, undergoing mammography more often than once every 2 years was more frequent among women reporting a high cancer risk perception than among those reporting a low–moderate cancer risk perception for breast cancer development (63% vs. 26%; OR: 12.0; 95% CI: 1 to 148.1). In addition, slightly more ovarian cancer screening exams were attended by noncarriers from *BRCA1* mutation–positive families (18% and 12% respectively for pelvic or transvaginal ultrasonography and CA125 testing) than by noncarriers from *BRCA2* mutation–positive families (15% and 8% respectively); however, those differences were not statistically significant.

DISCUSSION AND CONCLUSIONS

The present study is the first to describe actual breast and ovarian cancer screening behaviours among *BRCA1/2* mutation–negative women in real-world conditions and over a lengthy period (self-reported data could be provided for periods up to 10 years). On the whole, the findings do not show as many "excessive" practices as reported in previous studies[20–24], most of which were carried out among research cohorts. Screening practices by our participants were, for the most part, consistent with the guidelines established for women in the general population[30,31]. Breast cancer screening consisted primarily of mammography, and it targeted women from about the age of 40, and mostly those 50 years of age and older. Moreover, when participants used screening exams not recommended for women in the general population or at frequencies higher than advisable, those practices were, in most cases, related to a family history of breast or ovarian cancer.

TABLE III Associations of family history of breast and ovarian cancer with the extent of cancer screening practices

Screening practice	First-degree family history							
	Breast cancer				Ovarian cancer			
	0 Tests [*n* (%)]	≥1 Test [*n* (%)]	OR[a]	95% CI	0 Tests [*n* (%)]	≥1 Test [*n* (%)]	OR[a]	95% CI
Mammography, 30–39 years (≥1 since test result)	2 (8)	13 (38)	5.4	1 to 28.2	13 (27)	2 (22)	0.8	0.1 to 4.3
Mammography, 40–49 years (>1 every 2 years)	8 (24)	16 (36)	2.6	0.9 to 8	19 (31)	5 (31)	1.1	0.3 to 4
Mammography, 50–69 years (>1 every 2 years)	12 (33)	47 (60)	5.8	1.4 to 25	41 (50)	18 (55)	1	0.3 to 3.6
Breast ultrasonography (≥1 since test result)	6 (7)	28 (21)	4.1	1.3 to 12.6	24 (14)	10 (19)	1.4	0.6 to 3.1
Breast magnetic resonance imaging (≥1 since test result)	1 (1)	17 (13)	12.6	1.1 to 146.6	14 (8)	4 (8)	0.9	0.3 to 2.8
Pelvic or transvaginal ultrasonography (≥1 since test result)	9 (10)	27 (20)	2.3	1 to 5	20 (12)	16 (30)	2.9	1.1 to 7.5
Cancer antigen 125 (≥1 since test result)	8 (9)	14 (11)	1.2	0.5 to 3	9 (5)	13 (25)	7.3	2.6 to 20.9

[a] Adjusted for length of individual observation period, recruitment setting, and age at genetic test result disclosure (years).
OR = odds ratio; CI = confidence interval.

A positive association between the use of more mammography than recommended and a family history of breast cancer in first-degree relatives was found in participants 30–39 years of age and 50–69 years of age. Those results accord with assumptions suggesting that screening behaviours by noncarriers can be strongly influenced by their family history of cancer[21,22,24,32]. Although the mechanism by which family history influences screening behaviours in noncarriers remains unknown, those women—or their physicians—might have asked for or prescribed mammography earlier or more often than expected. Other factors such as cancer risk perception might play a role in the effect of family history on screening practices. Indeed, some authors suggest that an overestimation of cancer risk, increased pessimism, and feelings of self-vulnerability can be involved in the decision made by noncarriers less than 40 years of age to ask for more screening measures[20,33].

It remains difficult to make any statement about the screening behaviours of participants 40–49 years of age. At the time during which the participants in the present study were surveyed, Canadian recommendations did not support the inclusion of mammography screening in, or its exclusion from, the periodic health examination for women 40–49 years of age[30,34]. However, the last guidelines for Canada (published in 2011) recommend against routine breast screening for that age group[35]. In other countries, and especially in the United States, current screening guidelines concerning women 40–49 years of age also lack clarity. Various organizations disagree about whether population-based mammography should begin at the age of 40 or 50 years[36–46], and controversies about the issue can be seen in both the medical literature and the mass media[24,47–53]. According to the most recent U.S. recommendations applicable to women in the general population, mammography use before the age of 50 should be an individual decision that takes into account the patient's background and her values and preferences with respect to the advantages and drawbacks associated with the exam[54]. However, in light of the novel finding of the younger age of proven noncarriers at diagnosis of breast cancer, some guidelines indicate that screening at 40 years of age rather than later could be warranted based on the statistically and clinically relevant risk in those women[19]. Consequently, even though the findings in our study indicate that nearly 2 of 3 participants in their 40s underwent mammography every 2 years on average, that frequency cannot be considered "excessive," as reported by other studies carried out in women in that age group[20–24].

Furthermore, 11% of participants 50 years of age and older had undergone no mammography exams since the disclosure of their genetic test result. Given that about 80% of those women perceived their own risk of breast cancer to be low, they might have been falsely reassured by the result of their genetic test and could have become less vigilant about screening[25–27].

Very few studies have focused on the use of breast ultrasonography and MRI by *BRCA1/2* mutation–negative women[23,24,55]. The findings of the present study indicate that, compared with mammography, such exams are rarely used—which is not surprising, given they are not recommended for women in the general population[30,31]. The use of those breast cancer screening measures by some participants is also associated with a family history

of breast cancer. Ovarian cancer screening is also not recommended for women in the general population[56,57] because of the sparse evidence-based results about its efficacy and the high number of false-positive and false-negative results generated[56,58]. As expected, most participants did not undergo screening tests for ovarian cancer. Only a small proportion underwent pelvic or transvaginal ultrasonography and CA125 testing, and that at very low frequencies. Contrary to reports emerging from earlier studies[22–24,55], no screening overuse is evident in the present study. Our findings also suggest that use of screening exams is highly related to a family history of ovarian cancer. Because *BRCA1* mutations confer a higher risk of ovarian cancer than *BRCA2* mutations do[59,60], it might be expected that more ovarian cancer screening exams would be performed in noncarriers from *BRCA1* mutation–positive families, but that assumption was not confirmed.

For the present study, we considered selection, information, and confusion biases, which we tried, as far as possible, to alleviate. The participation rate (63%) is more than acceptable given the duration of the individual observation periods, which reached 10 years for some participants. As in other studies, the sample is rather well-educated, but the education level is probably quite representative of the female population attending cancer genetics clinics. Furthermore, the fact that this study was performed in the four main cancer genetics clinics in the province of Quebec might have fostered the representativeness of the sample.

Screening practices were assessed based on self-report data, which might be considered a limitation. Given the scope of this study, the use of administrative data was not the method of choice, because only mammography data would have been available for the entire study period[61]. Moreover, it was important to distinguish tests for screening purposes from tests for diagnostic purposes, which is challenging to accomplish using administrative data. We addressed that concern by developing the "screening history diary," which provided the women with specific instructions to help them to classify screening and diagnostic exams with the most precision possible. Earlier studies did not make that distinction.

Based on the history calendar approach, the "screening history diary" also seeks to minimize recall difficulties by inciting participants to use flexible indicators responsive to their individual situation[62]. Nevertheless, self-report of cancer screening practices is not the most accurate way to determine cancer screening rates. Such reports are subject to memory bias, which generally overestimates exam frequency. That bias has been confirmed in a meta-analysis of thirty-seven studies[63] and cross-confirmed in numerous other studies[64–67], including even after *BRCA1/2* testing[68]. More recently, a Canadian Community Health Survey of Ontarians, pooling from 5 additional provincial-level health databases, found that the report-to-record ratio was persistently greater than 1, indicative of significant over-reporting[69]. Despite the fact that our data concerning the frequency of cancer screening are most likely overestimated, the yearly averages of screening exams as self-reported here remain within the expected screening boundaries for women in the general population, which is reassuring in the face of the potential for "excessive" cancer screening in female noncarriers from *BRCA1/2* mutation–positive families.

Finally, data were adjusted for a number of potentially confounding variables, but residual confounding remains possible.

In the absence of specific guidelines for breast and ovarian cancer screening for female noncarriers from *BRCA1/2* mutation–positive families, family history, single nucleotide polymorphisms, and other genetic variants could be used to better estimate risk and create tailored follow-up for these women. The potential for increased risk in some noncarriers makes it difficult to draw conclusions about possible "excessive" screening practices in this population group, because a higher test ratio could actually be the expression of the need for some women to be provided with individualized management. With that potential in mind, it would be relevant to develop decision-making tools that would allow noncarriers to participate in their follow-up, taking into account the benefits and disadvantages of breast and ovarian cancer screening.

In coming years, advances in genomics should be translated into more and more accurate cancer risk estimates for noncarriers. As has been the case for mutation-positive women, further studies will be needed to foster the development of interventions and tools that will allow for the optimal use of screening strategies by *BRCA1/2* mutation–negative women in accordance with their genetic status and family history.

ACKNOWLEDGMENTS

We thank the study participants for their contribution to this work. We also thank the following people for help and support: Stéphanie Côté, Bouchra Labraki, and Rachel Silva-Smith (recruitment); Claudia Côté (database and quality management); Éric Demers (statistical analyses); and Jude-Emmanuel Cléophat (revision of the manuscript).

The study was supported by the Quebec Breast Cancer Foundation. SG is a recipient of a Fonds d'enseignement et de recherche scholarship (Faculté de pharmacie, Université Laval). JS is holder of the Canada Research Chair in Oncogenetics.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Faculté de pharmacie, Université Laval, Québec; †Centre de recherche du CHU de Québec-Université Laval, Québec; ‡Departments of Human Genetics and Oncology, McGill University, Montreal; §Sir Mortimer B. Davis Jewish General Hospital, Montreal; ‖Faculté de médecine, Université de Montréal, Montréal; #Service de médecine génique, CHUM, Montréal; **Faculté de médecine, Université Laval, Québec; and ††Centre des maladies du sein Deschênes–Fabia, CHU de Québec–Université Laval, Québec.

REFERENCES

1. Berliner J, Fay A on behalf of the Practice Issues Subcommittee of the National Society of Genetic Counselors' Familial Cancer Risk Counseling Special Interest Group. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2007;16:241–60.

2. Domchek S, Gaudet M, Stopfer J, *et al.* Breast cancer risks in individuals testing negative for a known family mutation in *BRCA1* or *BRCA2*. *Breast Cancer Res Treat* 2010;119:409–14.
3. Kurian AW, Gong GD, John EM, *et al.* Breast cancer risk for noncarriers of family-specific *BRCA1* and *BRCA2* mutations: findings from the Breast Cancer Family Registry. *J Clin Oncol* 2011;29:4505–9.
4. Korde LA, Mueller CM, Loud JT, *et al.* No evidence of excess breast cancer risk among mutation-negative women from *BRCA* mutation–positive families. *Breast Cancer Res Treat* 2011;125:169–73.
5. Harvey S, Milne R, McLachlan S, *et al.* Prospective study of breast cancer risk for mutation negative women from *BRCA1* or *BRCA2* mutation positive families. *Breast Cancer Res Treat* 2011;130:1057–61.
6. Canadian Cancer Society. Screening for breast cancer [Web page]. Toronto, ON: Canadian Cancer Society; 2017. [Available at: http://www.cancer.ca/en/cancer-information/cancer-type/breast/screening/?region=on; cited 21 May 2016]
7. Vézina S on behalf of the Institut national de santé publique du Québec (INSPQ) and the Direction systèmes de soins et services (DSSS). *Les enjeux éthiques dans le Programme québécois de dépistage du cancer du sein*. Montreal, QC: DSSS, INSPQ; 2006.
8. Colditz GA, Willett WC, Hunter DJ, *et al.* Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. *JAMA* 1993;270:338–43. [Erratum in: *JAMA* 1993;270:1548]
9. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997;71:800–9.
10. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol* 2001;2:133–40.
11. Nkondjock A, Ghadirian P. Risk factors and risk reduction of breast cancer [French]. *Med Sci (Paris)* 2005;21:175–80.
12. Lasset C. Épidémiologie du cancer de l'ovaire. In: Guastalla JP, Ray-Coquard I, eds. *Les cancers ovariens.* Paris, France: Springer; 2006: 550.
13. Robson M. Do women remain at risk even if they do not inherit a familial *BRCA1/2* mutation? *J Clin Oncol* 2011;29:4477–8.
14. Smith A, Moran A, Boyd MC, *et al.* Phenocopies in *BRCA1* and *BRCA2* families: evidence for modifier genes and implications for screening. *J Med Genet* 2007;44:10–15.
15. Rowan E, Poll A, Narod SA. A prospective study of breast cancer risk in relatives of *BRCA1*/*BRCA2* mutation carriers. *J Med Genet* 2007;44:e89.
16. Gronwald J, Cybulski C, Lubinski J, Narod SA. Phenocopies in breast cancer 1 (*BRCA1*) families: implications for genetic counselling. *J Med Genet* 2007;44:e76.
17. Katki HA, Gail MH, Greene MH. Breast-cancer risk in *BRCA*-mutation-negative women from *BRCA*-mutation-positive families. *Lancet Oncol* 2007;8:1042–3.
18. Metcalfe KA, Finch A, Poll A, *et al.* Breast cancer risks in women with a family history of breast or ovarian cancer who have tested negative for a *BRCA1* or *BRCA2* mutation. *Br J Cancer* 2009;100:421–5.
19. Vos JR, de Bock GH, Teixeira N, *et al.* Proven non-carriers in *BRCA* families have an earlier age of onset of breast cancer. *Eur J Cancer* 2013;49:2101–6.
20. Claes E, Evers-Kiebooms G, Decruyenaere M, *et al.* Surveillance behavior and prophylactic surgery after predictive testing for hereditary breast/ovarian cancer. *Behav Med* 2005;31:93–105.
21. Dawson SJ, Price MA, Jenkins MA, *et al.* Cancer risk management practices of noncarriers within *BRCA1/2* mutation positive families in the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer. *J Clin Oncol* 2008;26:225–32.
22. Dorval M, Nogues C, Berthet P, *et al.* on behalf of the INHERIT *BRCA*s and the GENEPSO Cohort. Breast and ovarian cancer screening of non-carriers from *BRCA1/2* mutation-positive families: 2-year follow-up of cohorts from France and Quebec. *Eur J Hum Genet* 2011;19:494–9.
23. Julian-Reynier C, Mancini J, Mouret-Fourme E, *et al.* Cancer risk management strategies and perceptions of unaffected women 5 years after predictive genetic testing for *BRCA1/2* mutations. *Eur J Hum Genet* 2011;19:500–6.
24. Duprez C, Christophe V, Milhabet I, *et al.* Comparison of the screening practices of unaffected noncarriers under 40 and between 40 and 49 in *BRCA1/2* families. *J Genet Couns* 2013;22:469–81.
25. Watson M, Foster CL, Eeles R, *et al.* Psychosocial impact of breast/ovarian (*BRCA1/2*) cancer-predictive genetic testing in a UK multi-centre clinical cohort. *Br J Cancer* 2004;91:1787–94.
26. Foster C, Watson M, Eeles R, *et al.* on behalf of the Psychosocial Study Collaborators. Predictive genetic testing for *BRCA1/2* in a UK clinical cohort: three-year follow-up. *Br J Cancer* 2007;96:718–24.
27. Kinney AY, Simonsen SE, Baty BJ, *et al.* Risk reduction behaviors and provider communication following genetic counseling and *BRCA1* mutation testing in an African American kindred. *J Genet Couns* 2006;15:293–305.
28. Belli RF, Callegaro M. The emergence of calendar interviewing: a theoretical and empirical rationale. In: Belli RF, Stafford F, Alwin DF, eds. *Calendar and Time Diary Methods in Life Course Research*. Thousand Oaks, CA: Sage; 2009: 31–52.
29. Gurmankin Levy A, Shea J, Williams SV, Quistberg A, Armstrong K. Measuring perceptions of breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2006;15:1893–8.
30. Ringash J on behalf of the Canadian Task Force on Preventive Health Care. Preventive health care, 2001 update: screening mammography among women aged 40–49 years at average risk of breast cancer. *CMAJ* 2001;164:469–76.
31. Canadian Task Force on Preventive Health Care. Breast cancer guidelines. *CMAJ* 2012;184:921–2.
32. Pelletier S, Wong N, El Haffaf Z, *et al.* Clinical follow-up and breast and ovarian cancer screening of true *BRCA1/2* noncarriers: a qualitative investigation. *Genet Med* 2016;18:627–34.
33. Milhabet I, Duprez C, Krzeminski A, Christophe V. Cancer risk comparative perception and overscreening behaviours of non-carriers from *BRCA1/2* families. *Eur J Cancer Care (Engl)* 2013;22:540–8.
34. Health Quality Ontario. Screening mammography for women aged 40 to 49 years at average risk for breast cancer: an evidence-based analysis. *Ont Health Technol Assess Ser* 2007;7:1–32.
35. Tonelli M, Connor Gorber S, Joffres M, *et al.* on behalf of the Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40–74 years. *CMAJ* 2011;183:1991–2001.
36. AACR comments on mammography screening for women age 40 to 49. *Oncology (Williston Park)* 1997;11:368.
37. National Institutes of Health Consensus Development Conference statement: breast cancer screening for women ages 40–49, January 21–23, 1997. National Institutes of Health Consensus Development Panel. *J Natl Cancer Inst* 1997;89:1015–26.
38. Leitch AM, Dodd GD, Costanza M, *et al.* American Cancer Society guidelines for the early detection of breast cancer: update 1997. *CA Cancer J Clin* 1997;47:150–3.
39. U.S. Preventive Services Task Force. Screening for breast cancer: recommendations and rationale. *Ann Intern Med* 2002;137:344–6.

40. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;151:716–26. [Errata in: *Ann Intern Med* 2010;152:688 and *Ann Intern Med* 2010;152:199–200]
41. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin* 2009;59:27–41.
42. American College of Obstetricians–Gynecologists. Practice bulletin no. 122: breast cancer screening. *Obstet Gynecol* 2011;118:372–82.
43. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis*. Ver. 1.2016. Fort Washington, PA: NCCN; 2011. [Current version available online at: http://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf (free registration required); cited 19 January 2016]
44. Baker S, Wall M, Bloomfield A. Breast cancer screening for women aged 40 to 49 years—what does the evidence mean for New Zealand? *N Z Med J* 2005;118:U1628.
45. U.K. National Institute for Health and Care Excellence (NICE), National Collaborating Centre for Primary Care. *Familial Breast Cancer: The Classification and Care of Women at Risk of Familial Breast Cancer in Primary, Secondary and Tertiary Care: Update.* NICE Clinical Guideline 41. London, U.K.: Royal College of General Practitioners; 2006.
46. Evans DG, Graham J, O'Connell S, Arnold S, Fitzsimmons D. Familial breast cancer: summary of updated NICE guidance. *BMJ* 2013;346:f3829.
47. Fletcher SW, Elmore JG. Clinical practice. Mammographic screening for breast cancer. *N Engl J Med* 2003;348:1672–80.
48. Kopans DB. The 2009 US Preventive Services Task Force (USPSTF) guidelines are not supported by science: the scientific support for mammography screening. *Radiol Clin North Am* 2010;48:843–57.
49. Hendrick RE, Helvie MA. United States Preventive Services Task Force screening mammography recommendations: science ignored. *AJR Am J Roentgenol* 2011;196:W112–16.
50. Pace LE, He Y, Keating NL. Trends in mammography screening rates after publication of the 2009 US Preventive Services Task Force recommendations. *Cancer* 2013;119:2518–23.
51. Sharpe RE Jr, Levin DC, Parker L, Rao VM. The effect of the controversial US Preventive Services Task Force recommendations on the use of screening mammography. *J Am Coll Radiol* 2013;10:21–4.
52. Tria Tirona M. Breast cancer screening update. *Am Fam Physician* 2013;87:274–8.
53. Kadaoui N, Guay M, Baron G, St-Cerny J, Lemaire J. Breast cancer screening practices for women aged 35 to 49 and 70 and older. *Can Fam Physician* 2012;58:e47–53.
54. Siu AL on behalf of the U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2016;164:279–96.
55. Schwartz MD, Isaacs C, Graves KD, *et al.* Long-term outcomes of *BRCA1*/*BRCA2* testing: risk reduction and surveillance. *Cancer* 2012;118:510–17.
56. Gladstone CQ. Screening for ovarian cancer. In: Canadian Task Force on the Periodic Health Examination. *Canadian Guide to Clinical Preventive Health Care*. Ottawa, ON: Health Canada; 1994: 870–881.
57. Allen DM. Ovarian cancer screening. *CMAJ* 2005;172:447.
58. Horsman D, Wilson BJ, Avard D, *et al.* on behalf of the National Hereditary Cancer Task Force. Clinical management recommendations for surveillance and risk-reduction strategies for hereditary breast and ovarian cancer among individuals carrying a deleterious *BRCA1* or *BRCA2* mutation. *J Obstet Gynaecol Can* 2007;29:45–60.
59. La Vecchia C. Epidemiology of ovarian cancer: a summary review. *Eur J Cancer Prev* 2001;10:125–9.
60. Antoniou A, Pharoah PD, Narod S, *et al.* Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117–30.
61. Larouche G, Chiquette J, Plante M, Pelletier S, Simard J, Dorval M. Usefulness of Canadian public health insurance administrative databases to assess breast and ovarian cancer screening imaging technologies for *BRCA1*/*2* mutation carriers. *Can Assoc Radiol J* 2016;67:308–12.
62. Glasner T, van der Vaart W. Applications of calendar instruments in social surveys: a review. *Qual Quant* 2009;43:333–49.
63. Howard M, Agarwal G, Lytwyn A. Accuracy of self-reports of Pap and mammography screening compared to medical record: a meta-analysis. *Cancer Causes Control* 2009;20:1–13.
64. Wang L, Jason XN, Upshur RE. Determining use of preventive health care in Ontario: comparison of rates of 3 maneuvers in administrative and survey data. *Can Fam Physician* 2009;55:178–9.e5.
65. Khoja S, McGregor SE, Hilsden RJ. Validation of self-reported history of colorectal cancer screening. *Can Fam Physician* 2007;53:1192–7.
66. Fehringer G, Howlett R, Cotterchio M, Klar N, Majpruz-Moat V, Mai V. Comparison of Papanicolaou (Pap) test rates across Ontario and factors associated with cervical screening. *Can J Public Health* 2005;96:140–4.
67. Ferrante JM, Ohman-Strickland P, Hahn KA, *et al.* Self-report versus medical records for assessing cancer-preventive services delivery. *Cancer Epidemiol Biomarkers Prev* 2008;17:2987–94.
68. Larouche G, Bouchard K, Chiquette J, Desbiens C, Simard J, Dorval M. Self-reported mammography use following *BRCA1*/*2* genetic testing may be overestimated. *Fam Cancer* 2012;11:27–32.
69. Lofters A, Vahabi M, Glazier RH. The validity of self-reported cancer screening history and the role of social disadvantage in Ontario, Canada. *BMC Public Health* 2015;15:28.