Published in final edited form as:

Ann Surg Oncol. 2013 November ; 20(12): 3817–3822. doi:10.1245/s10434-013-3040-4.

International Rates of Breast Reconstruction After Prophylactic Mastectomy in *BRCA1* and *BRCA2* Mutation Carriers

John Semple, MD¹, Kelly A. Metcalfe, RN, PhD^{1,2}, Henry T. Lynch, MD³, Charmaine Kim-Sing, MD⁴, Leigha Senter, MS, CGC⁵, Tuya Pal, MD⁶, Peter Ainsworth, MD⁷, Jan Lubinski, MD, PhD⁸, Nadine Tung, MD⁹, Charis Eng, MD, PhD^{10,11,12,13}, Donna Gilchrist, MD¹⁴, Joanne Blum, MD, PhD¹⁵, Susan L. Neuhausen, PhD¹⁶, Christian F. Singer, MD¹⁷, Parviz Ghadirian, PhD¹⁸, Ping Sun, PhD¹, Steven A. Narod, MD¹, and The Hereditary Breast Cancer Clinical Study Group

¹Women's College Research Institute, Toronto, ON, Canada ²Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, ON, Canada ³Department of Preventive Medicine and Public Health, Creighton University School of Medicine, Omaha, NE ⁴BC Cancer Agency, Vancouver, BC, Canada ⁵Division of Human Genetics, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH ⁶Moffitt Cancer Center, Tampa, FL ⁷London Regional Cancer Program, London, ON, Canada ⁸Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland ⁹Beth Israel Deaconess Hospital, Boston, MA ¹⁰Genomic Medicine Institute and Center for Personalized Genetic Healthcare, Cleveland, OH ¹¹Taussig Cancer Institute, Cleveland, OH ¹²Cleveland Clinic, Stanley Shalom Zielony Institute of Nursing Excellence, Cleveland, OH ¹³Department of Genetics and Genome Sciences, and CASE Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH ¹⁴Department of Medicine Genetics, University of Alberta, Edmonton, AB, Canada ¹⁵Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX ¹⁶Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA ¹⁷Department of Obstetrics and Gynecology and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria ¹⁸University of Montreal, Montreal, QC, Canada

Abstract

Background—Breast reconstruction is an option for women with *BRCA1* or *BRCA2* mutations who elect to undergo prophylactic mastectomy to prevent breast cancer. We report on the uptake of breast reconstruction after prophylactic mastectomy in women with *BRCA* mutations from eight countries.

Methods—Women with a *BRCA1* or *BRCA2* mutation were questioned regarding their cancer preventive practices. Information was recorded on prophylactic mastectomy and breast reconstruction.

K. A. Metcalfe, RN, PhD, kelly.metcalfe@utoronto.ca.

The members of The Hereditary Breast Cancer Clinical study group are listed in the Appendix.

DISCLOSURE The authors declare no conflict of interest.

Results—A total of 1,635 women with a *BRCA1* or *BRCA2* mutation who elected to undergo prophylactic mastectomy from eight countries were included. A total of 1,137 women (69.5 %) had breast reconstruction after prophylactic mastectomy. A total of 58.7 % of women over the age of 45 years at the time of prophylactic mastectomy had breast reconstruction compared to 77.6 % of women 35 years of age or younger [odds ratio (OR) 0.36, 95 % confidence interval (CI) 0.26–0.50, $p < 0.001$]. In addition, 62.9 % of women with a breast cancer diagnosis (contralateral prophylactic mastectomy) had breast reconstruction after prophylactic mastectomy compared to 79.7 % of women without a previous breast cancer diagnosis (OR 0.48, 95 % CI 0.38–0.61, $p < 0.001$). A total of 66.9 % of women from Canada had breast reconstruction after mastectomy compared to 71.9 % of American women (OR 0.75, 95 % CI 0.59–0.96, $p = 0.02$).

Conclusions—The majority of women elect for breast reconstruction after prophylactic mastectomy. However, younger women and those without a previous diagnosis of breast cancer are more likely to have breast reconstruction than older women or those with a previous diagnosis of cancer.

A woman with a *BRCA1* or *BRCA2* mutation has up to an 80 % lifetime risk of developing breast cancer, and once diagnosed with breast cancer, has a 40 % lifetime risk of developing a contralateral breast cancer.^{1–4} For these women, prophylactic mastectomy is an option to reduce the risk of a first primary breast cancer or a subsequent contralateral breast cancer. For women with a *BRCA* mutation without breast cancer, bilateral prophylactic mastectomy offers at least an 87 % breast cancer risk reduction, and for those with a previous diagnosis of breast cancer, contra-lateral prophylactic mastectomy offers a 97 % risk reduction of developing a contralateral breast cancer.^{4,5}

For those who elect for prophylactic mastectomy, breast reconstruction is an option. Little is known about the uptake of breast reconstruction after prophylactic mastectomy, including the predictors of uptake. Previous research in women with breast cancer undergoing mastectomy for surgical treatment has demonstrated that there are differences in uptake of breast reconstruction by country, age, and clinical features.^{6–10} However, it is unclear if the same predictors would be observed in women undergoing prophylactic mastectomy.

We have recently shown in a large international study that there are great differences in uptake of cancer preventive procedures by *BRCA1* and *BRCA2* mutation carriers in various countries.¹¹ In a cohort of 2,677 women with a *BRCA* mutation, we observed rates of uptake of prophylactic mastectomy ranging from 3 to 36 %, depending on the country of residence. It is not known if the same is true for breast reconstruction after prophylactic mastectomy. In the current study, we report on uptake of breast reconstruction after prophylactic mastectomy in *BRCA* mutation carriers from eight countries.

METHODS

Study Population

Eligible subjects were drawn from a database of carriers of deleterious mutations in either the *BRCA1* or the *BRCA2* gene. These women have been assessed for genetic risk at 57 centers within eight countries (Austria, Canada, China, France, Italy, Norway, Poland, and the United States) and were found to carry a *BRCA1* or *BRCA2* mutation. All study subjects

provided written informed consent for genetic testing. The study has been approved by the ethics committees of all participating centers. Subjects were eligible for this study if they were known to be a *BRCA1* or *BRCA2* mutation carrier and were older than 18 years. We studied both unaffected and affected women with breast cancer.

Procedures

Subjects completed a baseline questionnaire at the time of genetic testing, which assessed cancer history, breast cancer surgeries, and uptake of cancer prevention options (including prophylactic mastectomy) and breast reconstruction. Biannual follow-up questionnaires were administered by telephone or by mail. Questions assessed new diagnoses of breast cancer, breast cancer surgeries, and uptake of various cancer preventive options, including prophylactic surgery and breast reconstruction. The questionnaire is available upon request.

Statistical Analysis

The Chi square test was used to compare frequencies of categorical variables, such as differences in uptake of breast reconstruction among regions, and ANOVA was used to compare the mean values of continuous variables among different regions. Odds ratios were estimated by unconditional logistic regression. All statistical tests were performed by statistical software (SAS version 9.1.3, SAS Institute, Cary, NC, USA).

RESULTS

Demographics

Within the international database, 1,635 women with a *BRCA1* or *BRCA2* mutation from eight countries had a prophylactic mastectomy. Of those, 990 women (60.6 %) had a previous diagnosis of unilateral breast cancer and underwent a contralateral prophylactic mastectomy, and 645 women (39.4 %) had a bilateral prophylactic mastectomy for prevention of breast cancer. The mean age of the women at the time of prophylactic mastectomy was 44.5 years (range 23–79 years) for those with breast cancer and 42.5 years (range 20–77 years) for those with no previous diagnosis of breast cancer ($p < 0.0001$). For those with breast cancer, the mean time between diagnosis (first surgery) and prophylactic mastectomy was 3.2 years.

Table 1 presents the total number of prophylactic mastectomies by country. Rates of breast reconstruction after prophylactic mastectomy by country ranged from 50.0 % (in China) to 85.7 % (in France). Overall, 1,137 women (69.1 %) had breast reconstruction after prophylactic mastectomy. Of the 1,137 women with breast reconstruction after prophylactic mastectomy, 824 (72.5 %) had implants (either silicone or saline), 241 (21.2 %) had autologous reconstruction, and 62 (5.5 %) had a combined procedure (implant plus autologous) (0.8 % unknown).

Predictors of Breast Reconstruction After Prophylactic Mastectomy

Age at time of prophylactic mastectomy was examined as a possible predictor of breast reconstruction after prophylactic mastectomy. The mean age at time of prophylactic mastectomy for those who had breast reconstruction was 42.3 years (range 20–71 years),

compared to a mean age at time of prophylactic mastectomy of 47.1 years (range 25–79 years) for those without breast reconstruction ($p < 0.0001$). After adjusting for cancer status, *BRCA* mutation, and country, there were significant differences in mean ages between the two groups. Women over the age of 45 years at the time of prophylactic mastectomy were 64 % less likely to have breast reconstruction compared to those 35 years of age or younger [odds ratio (OR) 0.36, 95 % confidence interval (CI) 0.26–0.50, $p < 0.001$] (Tables 2, 3).

Rates of breast reconstruction after prophylactic mastectomy were examined by breast cancer status. For the 990 women with a previous diagnosis of breast cancer, 62.9 % had breast reconstruction after prophylactic mastectomy, compared to 79.7 % of women with no previous breast cancer (OR 0.43, 95 % CI 0.34–0.55, $p < 0.001$). When we adjusted for age, *BRCA* mutation, and country, women with a breast cancer diagnosis were significantly less likely to have breast reconstruction after prophylactic mastectomy compared to women without a breast cancer diagnosis (OR 0.48, 95 % CI 0.38–0.61, $p < 0.001$) (Table 3).

Rates of reconstruction were then examined for only those women with breast cancer, by type of original breast cancer surgery (lumpectomy vs. mastectomy). Of the 314 women with lumpectomy as first cancer surgery followed by bilateral prophylactic mastectomy, 75.2 % had breast reconstruction. Of the 676 women with mastectomy for the surgical treatment of their breast cancer followed by contralateral prophylactic mastectomy, 57.1 % had breast reconstruction. After adjusting for age, *BRCA* mutation, and country, those with a lumpectomy as the initial surgical treatment for breast cancer were significantly more likely to have breast reconstruction after contralateral prophylactic mastectomy compared to those with mastectomy as their surgical treatment for breast cancer (OR 2.79, 95 % CI 2.02–3.85; $p < 0.001$) (Table 3).

A total of 664 women were included from Canada and 842 women from the United States; 129 women were from other countries in Europe (Austria, France, China, Italy, Norway, and Poland) (Table 1). In Canada, 66.9 % of the women had breast reconstruction after prophylactic mastectomy, compared to 71.9 % in the United States and 68.2 % in Europe. After adjusting for age, *BRCA* mutation, and cancer status, women in Canada were less likely to have breast reconstruction after prophylactic mastectomy compared to women in the United States (OR 0.75, 95 % CI 0.59–0.96, $p = 0.02$) (Table 1).

DISCUSSION

For women with a *BRCA1* or *BRCA2* mutation, prophylactic mastectomy is the option that offers the greatest protection against breast cancer, and it is increasing in popularity.^{11,12} Among women with breast cancer, the uptake of breast reconstruction is low.^{6–10,13} However, it is unclear if this is also true in women with prophylactic mastectomy. In this international study, we report on breast reconstruction after prophylactic mastectomy in women with a *BRCA1* or *BRCA2* mutation.

Overall, 69.1 % of the women with a *BRCA* mutation had breast reconstruction after prophylactic mastectomy. However, women with a previous breast cancer diagnosis were significantly less likely to have received breast reconstruction compared to those without

breast cancer (62.9 vs. 79.7 %). Although this difference existed by breast cancer status, it should be noted that the breast reconstruction uptake of 62.9 % is considerably higher than any previous international report of breast reconstruction rates after cancer-related mastectomy. International rates of breast reconstruction after mastectomy have ranged from 5 to 29 %.^{7–10,13–21} This suggests that a woman is more likely to have breast reconstruction if she is having a mastectomy for prophylaxis rather than for the treatment of breast cancer.

For those women with a previous diagnosis of cancer who underwent contralateral prophylactic mastectomy for the prevention of a contralateral breast cancer, the type of initial surgery for breast cancer (lumpectomy versus mastectomy) influenced the uptake of breast reconstruction. Even after controlling for age and country, women with a lumpectomy were almost three times more likely to have breast reconstruction after prophylactic mastectomy compared to women with a mastectomy as the initial surgical treatment. This could be explained by a woman's comfort and acceptance of body image associated with a previous mastectomy.

In the current international study, we have reported that women with a *BRCA1* or *BRCA2* mutation over the age of 45 years at the time of prophylactic mastectomy were 64 % less likely to have breast reconstruction compared to those 35 years of age or younger. Age has consistently been reported as a predictor of breast reconstruction for women having mastectomy for the surgical treatment for breast cancer.^{7–9,15–18,22,23} Older women are much less likely to receive breast reconstruction after mastectomy (both immediate and delayed). In addition, we have previously reported on uptake of breast reconstruction in 123 Canadian women after bilateral prophylactic mastectomy (between 1991 and 2001).²⁴ Seventy-four (60 %) of the women had reconstructive breast surgery. Women younger than 50 years old were more likely to have reconstructive surgery after mastectomy than women 50 years or older (67.3 vs. 32.0 %; $p = 0.002$).

We have previously reported that in women with a *BRCA1* or *BRCA2* mutation, there are significant differences in uptake of cancer preventive options by country of residence.^{11,25} This includes bilateral prophylactic mastectomy and unilateral prophylactic mastectomy.^{11,25} In the current study, we have also observed significant differences in breast reconstruction rates after prophylactic mastectomy by country. Women from Canada were 25 % less likely to have breast reconstruction than women from the United States, even after adjusting for age, cancer status, and *BRCA* mutation. Although there is no known previous report of breast reconstruction after prophylactic mastectomy by country, there are reports from various countries of breast reconstruction after mastectomy for cancer. This trend may follow what is observed in breast reconstruction rates after mastectomy in Canada and the United States. Although there is no recently published population-wide data on breast reconstruction rates in Canada, in 1995–1996, the rate of breast reconstruction was 7.7 %.¹³ This can be compared to American population-based reports of rates of breast reconstruction ranging from 8.5 to 29.2 %.^{14–21}

The findings reported in the current study represent clinical practice from 57 cancer genetics clinics from throughout the world. Although this is one of the largest known databases of *BRCA1* and *BRCA2* mutation carriers in the world, it may not be representative of the

practices throughout each of the countries represented here. In some countries, the total number of subjects included was small, and the subjects were from a single clinical center and therefore may not be representative.

Prophylactic mastectomy is an option for women with a *BRCA1* or *BRCA2* mutation. We found that the uptake of breast reconstruction after prophylactic mastectomy is considerably higher than what has previously been reported in women with a mastectomy for breast cancer. However, we have demonstrated that there are factors that influence the rate of breast reconstruction, including age and country of residence. Further research should examine why these differences exist.

ACKNOWLEDGMENT

Dr. John Semple is supported through the Canadian Breast Cancer Foundation (Ontario Chapter).

APPENDIX

Other members of the Hereditary Breast Cancer Clinical Study Group who contributed to the study: William D. Foulkes, Andrea Eisen, Ophira Ginsburg, Mary Daly, Dawna Gilchrist, Albert Chudley, Talia Donenberg, Beth Karlan, Jeffrey Weitzel, Dana Zakalik, Judy Garber, Edmond Lemire, Dominique Stoppa-Lyonnet, Olufunmilayo I. Olopade, Sofia Merajver, Howard Saal, Louise Bordeleau, Carey A. Cullinane, Wendy McKinnon, Marie Wood, Daniel Rayson, Wendy Meschino, Jane McLennan, Josephine Wagner Costalas, Pal Moller, Ava Kwong, Claudine Isaacs, Fergus Couch, Siranoush Manoukian, and Taya Fallen.

REFERENCES

1. Antoniou AC, Shenton A, Maher ER, et al. Parity and breast cancer risk among *BRCA1* and *BRCA2* mutation carriers. *Breast Cancer Res.* 2006; 8:R72. [PubMed: 17187672]
2. Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol.* 2007; 25:1329–33. [PubMed: 17416853]
3. Metcalfe K, Gershman S, Lynch HT, et al. Predictors of contra-lateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *Br J Cancer.* 2011; 104:1384–92. [PubMed: 21487411]
4. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *J Clin Oncol.* 2004; 22:2328–35. [PubMed: 15197194]
5. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers. *J Natl Cancer Inst.* 2001; 93:1633–7. [PubMed: 11698567]
6. Alderman AK, Hawley ST, Janz NK, et al. Racial and ethnic disparities in the use of postmastectomy breast reconstruction: results from a population-based study. *J Clin Oncol.* 2009; 27:5325–30. [PubMed: 19805680]
7. Hall SE, Holman CD. Inequalities in breast cancer reconstructive surgery according to social and locational status in Western Australia. *Eur J Surg Oncol.* 2003; 29:519–25. [PubMed: 12875859]
8. Hvilsum GB, Holmich LR, Frederiksen K, et al. Socioeconomic position and breast reconstruction in Danish women. *Acta Oncol.* 2011; 50:265–73. [PubMed: 21091086]
9. Jeevan R, Cromwell DA, Browne JP, et al. Regional variation in use of immediate breast reconstruction after mastectomy for breast cancer in England. *Eur J Surg Oncol.* 2010; 36:750–5. [PubMed: 20609551]
10. Yu KD, Di GH, Wu J, et al. Development and trends of surgical modalities for breast cancer in China: a review of 16-year data. *Ann Surg Oncol.* 2007; 14:2502–9. [PubMed: 17564750]

11. Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, et al. International variation in rates of uptake of preventive options in *BRCA1* and *BRCA2* mutation carriers. *Int J Cancer*. 2008; 122:2017–22. [PubMed: 18196574]
12. Metcalfe KA, Snyder C, Seidel J, et al. The use of preventive measures among healthy women who carry a *BRCA1* or *BRCA2* mutation. *Fam Cancer*. 2005; 4:97–103. [PubMed: 15951959]
13. Baxter N, Goel V, Semple JL. Rates and regional variation of breast reconstruction following mastectomy for breast cancer: viewpoint from a single payer medical system. 2002
14. Polednak AP. Postmastectomy breast reconstruction in Connecticut: trends and predictors. *Plast Reconstr Surg*. 1999; 104:669–73. [PubMed: 10456516]
15. Alderman AK, McMahon L Jr, Wilkins EG. The national utilization of immediate and early delayed breast reconstruction and the effect of sociodemographic factors. *Plast Reconstr Surg*. 2003; 111:695–703. [PubMed: 12560690]
16. Polednak AP. How frequent is postmastectomy breast reconstructive surgery? A study linking two statewide databases. *Plast Reconstr Surg*. 2001; 108:73–7. [PubMed: 11420507]
17. Alderman AK, Wei Y, Birkmeyer JD. Use of breast reconstruction after mastectomy following the Women's Health and Cancer Rights Act. *JAMA*. 2006; 295:387–8. [PubMed: 16434628]
18. Joslyn SA. Patterns of care for immediate and early delayed breast reconstruction following mastectomy. *Plast Reconstr Surg*. 2005; 115:1289–96. [PubMed: 15809588]
19. Rosson GD, Singh NK, Ahuja N, et al. Multilevel analysis of the impact of community vs patient factors on access to immediate breast reconstruction following mastectomy in Maryland. *Arch Surg*. 2008; 143:1076–81. [PubMed: 19015466]
20. Tseng WH, Stevenson TR, Canter RJ, et al. Sacramento area breast cancer epidemiology study: use of postmastectomy breast reconstruction along the rural-to-urban continuum. *Plast Reconstr Surg*. 2010; 126:1815–24. [PubMed: 21124121]
21. Kruper L, Holt A, Xu XX, et al. Disparities in reconstruction rates after mastectomy: patterns of care and factors associated with the use of breast reconstruction in Southern California. *Ann Surg Oncol*. 2011; 18:2158–65. [PubMed: 21308486]
22. Morrow M, Scott SK, Menck HR, et al. Factors influencing the use of breast reconstruction postmastectomy: a National Cancer Data Base study. *J Am Coll Surg*. 2001; 192:1–8. [PubMed: 11192909]
23. Tseng JF, Kronowitz SJ, Sun CC, et al. The effect of ethnicity on immediate reconstruction rates after mastectomy for breast cancer. *Cancer*. 2004; 101:1514–23. [PubMed: 15378473]
24. Metcalfe KA, Goel V, Lickley L, et al. Prophylactic bilateral mastectomy: patterns of practice. *Cancer*. 2002; 95:236–42. [PubMed: 12124821]
25. Metcalfe KA, Lubinski J, Ghadirian P, et al. Predictors of contralateral prophylactic mastectomy in women with a *BRCA1* or *BRCA2* mutation: the Hereditary Breast Cancer Clinical Study Group. *J Clin Oncol*. 2008; 26:1093–7. [PubMed: 18195327]

TABLE 1

Reconstruction by country and groups

Country	Total no.	Subject groups n (%)			Reconstructions, n (%)
		Bilateral PM (no cancer)	Contralateral PM after mastectomy	Contralateral PM after lumpectomy	
Austria	26	10 (38.5)	8 (30.8)	8 (30.8)	15 (57.5)
Canada	664	293 (44.1)	217 (31.8)	154 (23.2)	444 (66.9)
France	7	1 (14.3)	2 (28.6)	4 (57.1)	6 (85.7)
Hong Kong, China	6	1 (14.9)	5 (83.3)	0	3 (50)
Italy	17	3 (17.7)	10 (58.8)	4 (23.5)	14 (82.4)
Norway	10	8 (80.0)	2 (20.0)	0	8 (80.0)
Poland	63	19 (30.2)	40 (63.5)	4 (6.4)	42 (66.7)
United States	842	310 (36.8)	392 (46.6)	140 (16.6)	605 (71.9)
Total	1,635	645	676	314	
Total no. of reconstructions	1,137	514 (79.7 %)	387 (57.1 %)	236 (75.2 %)	1,137 (69.1)

PM prophylactic mastectomy

Table 2

Breast reconstruction uptake by group

Variable	<i>n</i>	Breast reconstruction <i>n</i> (%)	<i>p</i>
Cancer status			
No breast cancer	645	514 (79.7)	
Breast cancer	990	623 (62.9)	<0.0001
Breast cancer surgery			
PM after mastectomy	676	387 (57.3)	
PM after lumpectomy	314	236 (75.2)	<0.0001
<i>BRCA</i> mutation			
<i>BRCA1</i>	1,045	732 (70.1)	
<i>BRCA2</i>	547	374 (68.4)	
Both	9	7 (77.8)	0.34
Unknown	34	24 (70.6)	
Patient age at PM			
< 35 years	294	228 (77.6)	
36–45 years	716	542 (75.7)	<0.0001
> 45 years	625	367 (58.7)	
Country			
United States	824	605 (71.9)	
Canada	664	444 (66.9)	
Europe	129	88 (68.2)	0.11

PM prophylactic mastectomy

Table 3

Comparison of uptake of breast reconstruction by various factors

Variable	Univariate analysis		Multivariate analysis ^a	
	OR (95% CI)	P	OR (95% CI)	P
Cancer status				
No breast cancer	1		1	
Breast cancer	0.43 (0.34–0.54)	<0.0001	0.48 (0.38–0.61)	<0.0001
Breast cancer surgery				
PM after mastectomy	1		1	
PM after lumpectomy	2.26 (1.68–3.04)	<0.0001	2.79 (2.02–3.85)	<0.0001
BRCA mutation				
BRCA1	1		1	
BRCA2	0.92 (0.74–1.16)	0.49	1.04 (0.82–1.29)	0.91
Age at PM				
< 35 years	1		1	
36–15 years	0.78 (0.57–1.08)	0.13	0.78 (0.56–1.09)	0.14
>45 years	0.37 (0.27–0.51)	<0.0001	0.36 (0.26–0.50)	<0.0001
Trend in the three groups	0.57 (0.49–0.67)	<0.0001	0.57 (0.49–0.67)	<0.0001
Trend per year	0.95 (0.94–0.96)	<0.0001	0.95 (0.94–0.96)	<0.0001
Country				
United States	1		1	
Canada	0.79 (0.63–0.99)	0.04	0.75 (0.59–0.96)	0.02
Europe	1.19 (0.80–1.77)	0.40	1.14 (0.74–1.71)	0.55

OR odds ratio, CI confidence interval, PM prophylactic mastectomy

^a Adjusted for all the variables