

Occult cancer: suspected breast and *BRCA* gene mutations

Mollie L. Hutton, MS, CGC,¹ Nicoleta C. Voian, MD, MPH,² and Carolyn D. Farrell, MS, CNP, CGC¹

¹Roswell Park Cancer Institute, Buffalo, New York; ²State University of New York, Buffalo School of Medicine

Currently, the best means of managing and preventing breast cancer is through early detection and identification of women who are at significantly increased risk for the disease. Those who are at increased risk are candidates for genetic testing involving the *BRCA1* and *BRCA2* genes. However, those who present with an occult cancer present a significant challenge in regard to etiology, which can have an impact on decisions about cancer risk management. We report here on two cases demonstrating an association between occult cancer, with suspected breast primary, and the presence of a *BRCA* gene mutation. These cases draw attention to the fact that occurrences of occult cancer, in particular those with a suspected breast primary, warrant consideration of genetic testing for possible mutations in the *BRCA1* and *BRCA2* genes. This is especially important as identification of a mutation will impact secondary cancer risk and medical management decisions.

Currently, the best means of evaluating and preventing breast cancer is through early detection and the identification of women who are at significantly increased risk for the disease. Mutations in the *BRCA1* and *BRCA2* genes remain the most commonly known causes of hereditary breast and ovarian cancer. Women with mutations in either the *BRCA1* or *BRCA2* genes are known to be at significantly increased lifetime risk for breast and ovarian cancer, which includes risk for multiple primary tumors. Knowledge of this risk can be vitally important to risk management decisions as well as treatment decisions in the event of a cancer diagnosis.

The National Comprehensive Cancer Network guidelines on Genetics/Familial High-Risk Assessment: Breast and Ovarian Cancer identify women with different combinations of personal and/or family histories of breast and ovarian cancer as being candidates for genetic evaluation and testing; however, these guidelines do not address situations of occult findings. We argue that a woman who has been identified with an occult malignancy should also be considered for genetic evaluation and testing. This is because identification of a *BRCA1* or *BRCA2* mutation (or other hereditary cancer gene mutation) would confirm the likely etiology of the occult finding and pos-

sibly affect treatment decisions and future cancer risk and associated management decisions, which could include considerations for more frequent screening and/or prophylactic surgery. This article presents 2 cases of occult breast cancer associated with mutations in the *BRCA* genes as supporting evidence of the importance of including genetic evaluation in the workup for occult malignancies.

Case 1

Patient. A 41-year-old white woman diagnosed with a left axillary cancer.

Evaluation. Screening mammogram, ultrasound, PET scan, and MRI were negative for a primary breast tumor; Cancer Antigen 27.29 was within normal range.

Past medical history. Age 12 years at menarche, no pregnancies, no prior breast biopsies, no history of oral contraceptive (OCP) use.

Family history (Figure 1). Patient reported being of Italian ancestry maternally and German, Italian, Irish, and Prussian ancestry paternally. Maternal family history included breast cancer in 2 great aunts (in their 60s and 70s), lung and adrenal cancers in a great uncle (in his 50s or 60s; with history of smoking) and 5 first cousins once-removed with histories including leukemia, cervical, colon, lung (in a smoker), esophageal and

Manuscript received August 23, 2011; accepted May 23, 2012.

Correspondence Mollie L. Hutton, MS, CGC, Roswell Park Cancer Institute, Elm & Carter Streets, Buffalo, NY 14263 (Mollie.Hutton@Roswellpark.org).

Disclosures The authors have no financial disclosures.

Commun Oncol 2013;10:202-208 © 2013 Frontline Medical Communications
DOI: 10.12788/j.cmonc.0018

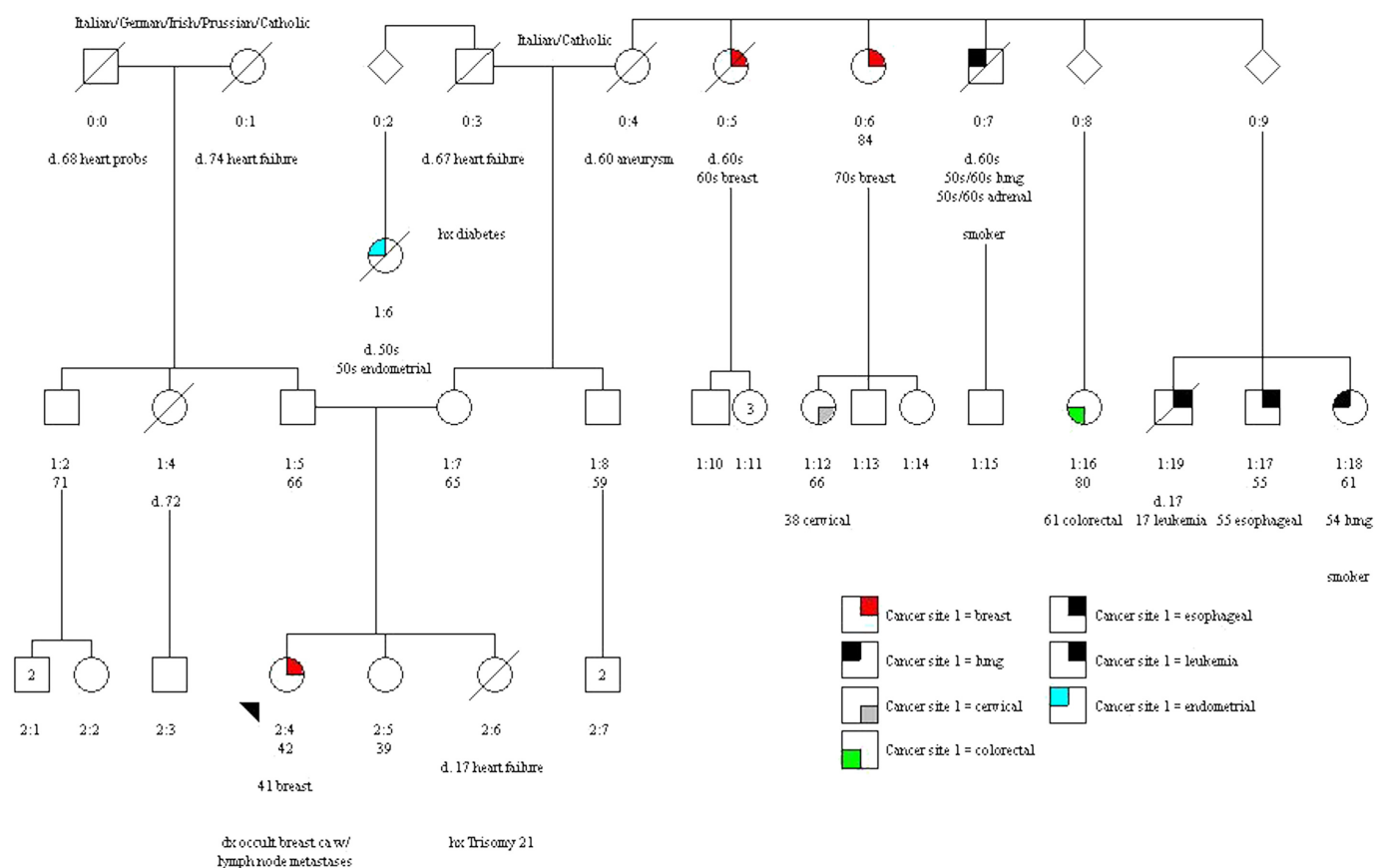


FIGURE 1 Pedigree corresponding to Case 1. Arrow depicts patient described in case report.

TABLE 1 Risk of developing breast cancer^a and likelihood of identifying a BRCA1 or BRCA2 gene mutation

Cancer status	Risk of developing breast cancer, %				Likelihood of a BRCA gene mutation, %					
	Gail	Claus	IBIS	BOADICEA	MGL tables ^b	BRCAPro	IBIS	BOADICEA		
1 year before diagnosis	11.6	NCP	10.9	8.02	1.5	0.1	BRCA1 0.017	BRCA2 0.023	BRCA1 0.04	BRCA2 0.09
After diagnosis	NA	NA	NA	13.16 ^c	4.7	1.3 (0.7 ^d)	NA	0.58	0.83	

Abbreviations: BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; MGL, Myriad Genetic Laboratories; NA, not applicable; NCP, no calculation possible – relatives too distant.

^aUsing the Gail, Claus, IBIS, BOADICEA models; lifetime risk computed from perspective of 1 year before cancer diagnosis; ^bComputed using the Myriad Genetic Laboratories mutation likelihood model circa 2010; ^cRepresents risk for contralateral breast cancer; ^dIncludes consideration of ER/PR status in calculation.

endometrial cancers. There was no known paternal family history of cancer.

Predicted risk for developing breast cancer and BRCA mutation likelihood (Table 1). Several risk assessment models were used to develop estimates regarding the patient's risk for breast cancer (prior to her occult cancer diagnosis) and the likelihood for a BRCA gene mutation. The figures returned by all of the applied models predicted her likelihood of developing breast cancer to

be consistent with that of the general population (10%–12%). In addition, estimates regarding the likelihood of identifying a BRCA mutation in the patient were also similar to general population carrier frequencies (< 1%) and did not exceed 5%, even when calculated using her occult cancer diagnosis as a suspected breast primary.

Pathology and type of cancer diagnosed. Pathology from the left axillary biopsy showed a moderately differentiated adenocarcinoma, ER/PR positive, HER2/neu

negative, with 2 of 18 positive lymph nodes. TTF-1 immunostaining was performed and was negative. These features are compatible with a breast carcinoma as per interpretation noted in the pathology report.

The staging MRI and PET scans revealed a lesion in the left tricep. The results of a tricep needle biopsy showed myxoid spindle cell neoplasm consistent with intramuscular myxoma. A prophylactic bilateral mastectomy and bilateral salpingo-oophorectomy, done after genetic testing, did not show any evidence of malignancy. A primary tumor was never identified (related to her left axillary malignancy).

Nature of *BRCA* gene mutation identified. The patient was offered and proceeded with genetic testing for mutations in the *BRCA1* and *BRCA2* genes. A deleterious mutation in the *BRCA2* gene, specifically 6079del4, was identified. This *BRCA2* mutation results in premature truncation of the *BRCA2* protein at amino acid position 1961. It has been estimated that women with deleterious mutations in the *BRCA2* gene have as much as an 84% risk of breast cancer and a 27% risk of ovarian cancer by age 70.¹ Further, mutations in *BRCA2* have a reported association with secondary cancer risk equivalent to a 12% risk of a second breast cancer within 5 years of the first, and a 16% risk of subsequent ovarian cancer.^{2,3}

Case 2

Patient. A 32-year-old white woman diagnosed with a right axillary cancer.

Evaluation. Mammography and breast ultrasound revealed benign findings confirmed by needle biopsy. A CT scan of the abdomen was negative, a CT scan of the chest showed postoperative changes in the right axilla, and an MRI of the breast and PET scan were negative. (The patient was diagnosed with a contralateral breast cancer at age 35).

Past medical history. Age 11 years at menarche, oral contraceptive pills used for 14 years, had never been pregnant, and had no breast biopsies prior to diagnosis of breast cancer at age 32. She also had a history of hypothyroidism, dermatomyositis, GERD (gastroesophageal reflux disease), and epigastric hernia repair. The patient was diagnosed with a single adenomatous colorectal polyp at age 28, and 3 hyperplastic colorectal polyps at age 32. Genetic evaluation included consideration of familial adenomatous polyposis (FAP); however, she did not meet the eligibility criteria established by her insurance company for coverage of FAP-associated gene testing, even though an attenuated form of FAP (AFAP) can be associated with 20 or fewer colorectal polyps.⁴

Family history (Figure 2). The patient reported being of Italian and Spanish ancestry maternally and Polish and German ancestry paternally. Family history was signifi-

cant for leukemia in her paternal grandmother and breast cancer in a paternal great-aunt (diagnosed at an older age) and paternal great-grandmother (at an unknown age). The maternal family history included colon cancer in an uncle (in his 50s) and great grandfather (at an unknown age), as well as stomach cancer (at an unknown age) in her great grandmother.

Predicted risk for developing breast cancer and *BRCA* mutation likelihood (Table 2). In assessing the patient's likelihood for developing breast cancer, the standard risk assessment models estimated her risk (before her suspected breast cancer diagnosis) to be consistent with the general population risk. In addition, her estimated likelihood of having a *BRCA* mutation was consistent with general population mutation frequency when calculated before to her initial cancer diagnosis and was less than 10% (and less than 2%, based on one model) even after her initial cancer diagnosis. Only when calculating this patient's *BRCA* mutation likelihood given here 2 primary breast cancers did her mutation likelihood rise significantly above general population mutation frequency.

Pathology and type of cancer diagnosed. Right axillary mass pathology showed lobular carcinoma, ER/PR and HER2/neu negative. This triple negative hormone receptor status has been shown in some cases to be associated with a germline *BRCA1* gene mutation. At axillary dissection, the patient had 17 of 19 positive lymph nodes. Initially, the suspicion was of either a breast or gastrointestinal origin. Subsequent to this axillary finding, the patient underwent esophagogastroduodenoscopy and colonoscopy, which yielded benign findings (1 hyperplastic prepiloric polyp and 3 hyperplastic colorectal polyps). These findings excluded a gastrointestinal primary neoplasia, leaving the multidisciplinary team to consider the axillary mass as being associated with a breast primary. Following axillary dissection the patient was treated with chemotherapy and radiation.

The pathology of the contralateral breast cancer (diagnosed at age 35) showed infiltrating ductal carcinoma with associated DCIS (0/5 sentinel lymph nodes were positive). The patient proceeded with bilateral mastectomy prior to genetic testing. After genetic testing that identified a *BRCA1* gene mutation, the patient proceeded with prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lavage; all were negative for malignancy.

Nature of *BRCA* gene mutation identified. The patient was offered and proceeded with genetic testing for mutations in the *BRCA1* and *BRCA2* genes. A deleterious mutation in the *BRCA1* gene, specifically 187delAG, was identified. This *BRCA1* frameshift mutation results in a stop codon at amino acid position 39 of the *BRCA1* protein. Deleterious mutations in the *BRCA1* gene have

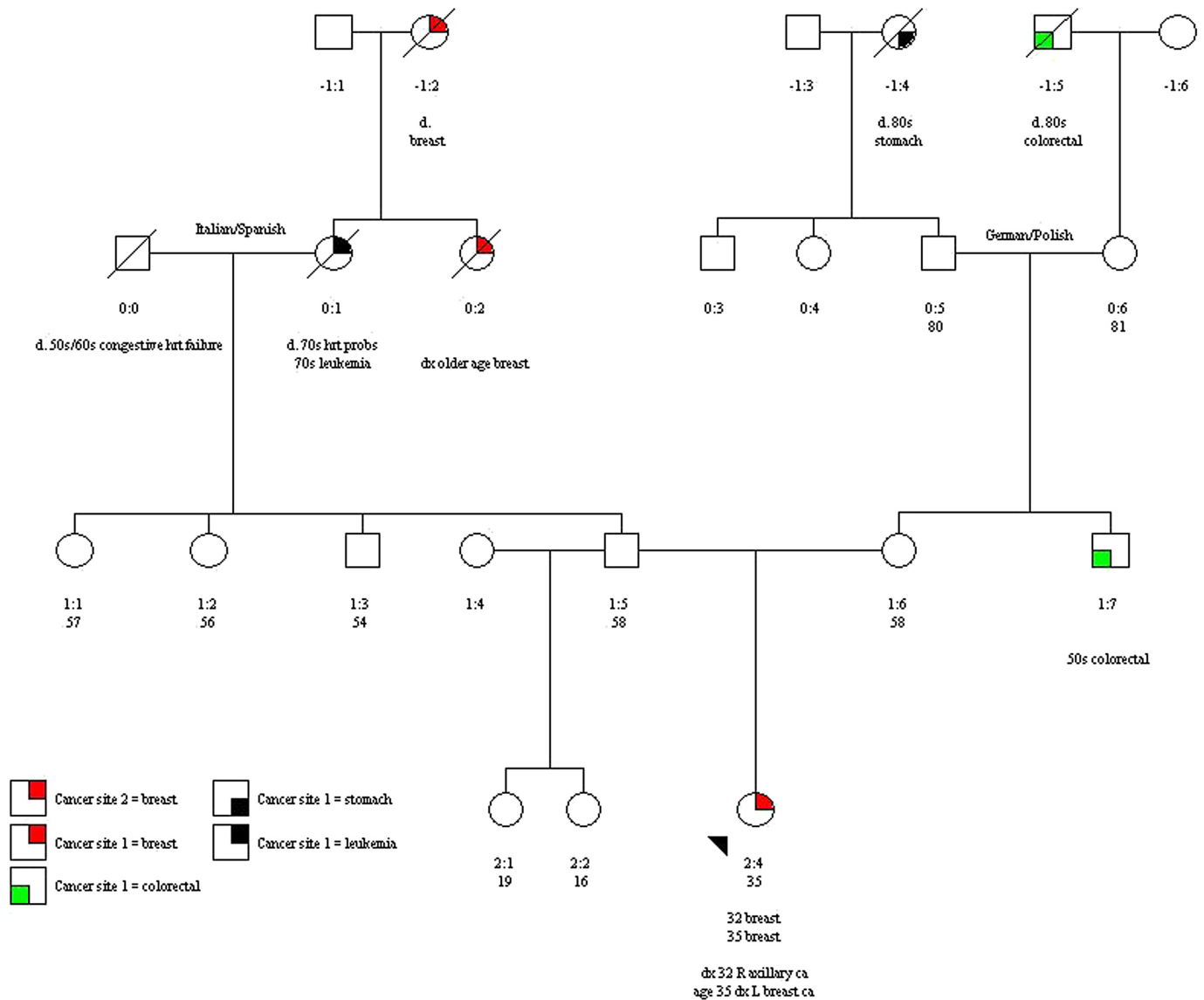


FIGURE 2 Pedigree corresponding to Case 2. Arrow depicts patient described in case report.

TABLE 2 Risk of developing breast cancer^a and likelihood of identifying a BRCA1 or BRCA2 gene mutation

Cancer status	Risk of developing breast cancer, %				Likelihood of a BRCA gene mutation, %					
	Gail	Claus	IBIS	BOADICEA	MGL tables ^b	BRCAPro	IBIS		BOADICEA	
1 year before diagnosis	12.9	NCP	10.58	8.58	1.5	0.1	BRCA1	BRCA2	BRCA1	BRCA2
							0.018	0.028	0.05	0.11
After first diagnosis	NA	NA	NA	17.54 ^c	4.7	2.8 (8.6 ^d)	NA	NA	1.48	1.66
After diagnosis of second breast cancer	NA	NA	NA	NA	4.7	41.5 (73.1 ^d)	NA	NA	20.73	14.07

Abbreviations: BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; MGL, Myriad Genetic Laboratories; NA, not applicable; NCP, no calculation possible – relatives too distant.
^aUsing the Gail, Claus, IBIS, and BOADICEA models; lifetime risk computed from perspective of 1 year before cancer diagnosis; ^bComputed using the Myriad Genetic Laboratories mutation likelihood model circa 2010; ^cRepresents risk for contralateral breast cancer; ^dIncludes consideration of ER/PR status in calculation.

been found to be associated with up to an 87% risk of breast cancer and 44% risk of ovarian cancer by age 70.⁵ In addition, *BRCA1* mutations have an associated risk for second primary cancers, including a 20% risk of a second breast cancer within 5 years of the first, as well as a 10-fold increase in the risk of subsequent ovarian cancer.^{6,7} This *BRCA1* mutation is an identified founder mutation in the Ashkenazi Jewish population.

Evaluation for occult cancer – suspected breast

An occult cancer that occurs in the axilla is considered a likely metastasis to the lymph nodes from a primary neoplastic tumor. The most common primary adenocarcinomas known to metastasize to axillary lymph nodes are breast, lung, thyroid, stomach, colorectal and pancreas.

Imaging

Upon diagnosis of an occult axillary cancer, the patient is a candidate for thorough workup including personal medical history, physical examination, screening blood work, and chest radiography. If the primary source of metastasis remains unknown, then extensive imaging techniques are used, including mammography, ultrasonography, computed tomography (CT) and/or MRI as these modalities can detect a primary tumor in the clinically uninvolved, yet suspected, breast. However, negative imaging findings do not exclude the breast as the primary site. In fact, studies have found that in about 16%-33.3% of cases, the primary tumor was never found, as in the situation of our cases.⁸⁻¹¹

Biochemical markers

Another approach for determining whether a breast primary exists includes testing for estrogen and progesterone receptor status (ER/PR) and analysis of lymph nodes. A positive ER and/or PR status is consistent with a primary breast cancer. Alternatively, a negative ER and/or PR status does not exclude the diagnosis of a primary breast cancer and in fact, still supports the possibility of a primary breast cancer. Studies have demonstrated that ER, PR, and HER2/neu negative status is associated with breast cancer in *BRCA1* gene mutation carriers.^{12,13} Estrogen and progesterone receptor levels are also used to assess and distinguish synchronous from metachronous tumors in bilateral breast cancers. Yirmibeşoğlu and colleagues reported a case with an occult breast cancer presenting with an axillary lymph node metastasis and a contralateral breast cancer. They noted that when the diagnosis of breast cancer is accompanied by a contralateral axillary lymphadenopathy, there is the possibility of a second occult breast cancer (in the contralateral breast), which is the primary site for the adenopathy. This dis-

inction is relevant because of differences in the therapeutic approach, but also because it relates to genetic risk in regard to metastatic disease versus multiple primary tumors, which warrants consideration of genetic testing.

Discussion

There are several models available for computing a woman's estimated risk of developing breast cancer and likelihood of a *BRCA* gene mutation. Because the methodologies used in most models for computing breast cancer risk apply to women without a personal history of breast cancer, the patients on whom we report here were not appropriate candidates for application of these models. However, we have retrospectively calculated their risk for breast cancer using these models based on their history 1 year prior to diagnosis of cancer to determine if they were considered at increased risk.

The most frequently used models are Gail and Claus, although the IBIS and BOADICEA models also provide risk estimates, with all 4 models taking into consideration different combinations of genetic and nongenetic factors. The Gail model takes into consideration the patient's age, race, history of breast biopsies, age at menarche, and history of breast cancer in first degree female relatives.¹⁴ The Claus model calculates risk based on family history of women with breast cancer, but also considers age at diagnosis as well as first and second degree, maternal and paternal, relatives.¹⁵ The IBIS Breast Cancer Risk Evaluation Tool incorporates family history factors (including breast and ovarian cancer) with nongenetic risk factors (such as age at menarche and reproductive history), as well as Ashkenazi Jewish ancestry to determine breast cancer and *BRCA* mutation risks.¹⁶ The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model incorporates family history of breast (male and female), ovarian, prostate, and pancreatic cancers and history of multiple cancers to calculate cancer risk (both breast and ovarian) and *BRCA* gene mutation likelihood based on data from 2 population-based studies in the United Kingdom.¹⁷

All 4 of these prediction models have limitations in their ability to provide an accurate risk estimate regarding the development of breast cancer. The Gail, Claus, and IBIS models are not applicable in women with a personal history of invasive breast cancer, DCIS, or LCIS (lobular carcinoma in situ). Neither do they take into consideration male breast cancer (although the BOADICEA model does). A strength of the IBIS and BOADICEA models is their ability to include family history through third degree relatives. The Gail model is limited to cancer history in only first degree relatives, and Claus extends only to second degree relatives. Furthermore, only the

IBIS and BOADICEA models consider mutation status in estimating cancer risk and allow for inclusion of a family history of ovarian cancer (and in the BOADICEA model other less common *BRCA* gene mutation-associated cancers). In addition, when calculating breast cancer risk, the Gail model does not take into account the ages of breast-cancer onset in a family or the existence of bilateral breast cancer. Thus, these models generate different figures for risk of breast cancer, have varying degrees of applicability on a case-by-case basis and/or may under-predict risk in women who have a limited family structure, or one or more factors that were not considered, as in both patients reported here.

Separately, models also exist to allow for estimation of the likelihood of identifying a *BRCA* gene mutation based on personal and family history, including the Myriad Genetic Laboratories (MGL) tables and BRCAPro, as well as IBIS and BOADICEA (as discussed previously, which also provide estimation of breast cancer risk). MGL publishes *BRCA* gene mutation prevalence tables based on personal and family history information received on blood samples sent for genetic testing in their laboratory. There are separate prevalence tables depending on whether the individual is of Ashkenazi Jewish ancestry or not.¹⁸ The MGL table (<http://www.myriad.com/lib/brac/brca-prevalence-tables.pdf>; circa 2010) was based on 162,914 observations; individuals for whom relevant personal and family history information were not provided to the laboratory were not included. The BRCAPro model is a computerized model for finding the probability of a *BRCA* mutation based on a woman's personal and family history of cancer. The 2 scientific bases for the BRCAPro model include incorporation of the autosomal dominant nature of inheritance with the *BRCA1* and *BRCA2* genes, as well as use of Bayes' rule for deriving the probability of a mutation, conditional on an individual's family history of cancer.^{19,20}

The MGL table, BRCAPro, IBIS, and BOADICEA models all calculated the likelihood of identifying a *BRCA* gene mutation in both cases presented here, prior to the patient's diagnoses of occult breast cancer, to be consistent with the mutation likelihood in the general population. In addition, even after their cancer diagnoses, only the MGL table and BRCAPro model returned mutation likelihoods above general population risk, and yet these mutation likelihoods were still less than 5%. Despite that, in both currently reported cases, a deleterious mutation was identified in one of the *BRCA* genes—*BRCA2* in Case 1, and *BRCA1* in Case 2. These findings suggest that in assessing an occult cancer with axillary involvement, especially in young women and when breast cancer is suspected, we need to consider genetic risk assessment and testing of the *BRCA 1* and *BRCA 2* genes.

Based on the different risk assessment models (for both breast cancer and gene mutation likelihoods) neither of the cases presented here would have been considered at high risk for developing breast cancer or be identified at hereditary risk for such. However, as shown, despite the risk assessment model's predictions, both cases were found to be associated with hereditary risk for cancer. Based on that finding, we would argue that it is important to consider potential hereditary risk beyond simply running risk assessment models or applying established testing guidelines in the situation of an occult malignancy because the limitations of those methods of identification could miss identifying potential hereditary risk in an occult cancer situation. Although we have discussed here occult cancer in the situation of a suspected breast primary, we would suggest that modification of evaluation for hereditary risk be considered in other occult primary situations, especially in the presence of an early age diagnosis, that is, younger than 50 years.

Conclusion

There is limited information in the medical literature on occult—suspected breast—cancers in the presence of a *BRCA* mutation. Both women in our case reports presented with axillary cancer, were suspected to have metastatic disease with breast being the likely primary tumor, and had an extensive workup including a multidisciplinary approach. Based on the young age at cancer diagnosis in both women, this raised consideration of possible genetic or hereditary cancer risk despite the otherwise unremarkable family history. Although their risk for breast cancer and/or likelihood of a *BRCA* gene mutation was statistically similar to that of the general population before their cancer diagnosis, and the mutation likelihood was still low after their (suspected) breast cancer diagnosis, their age at diagnosis coupled with the level of suspicion for a primary breast cancer supported proceeding with genetic evaluation and testing for mutations in the *BRCA* genes. Both women were positive for a deleterious *BRCA* gene mutation (1 in *BRCA1* and 1 in *BRCA2*), meaning that both women were at significantly increased risk for breast and ovarian cancers. Thus genetic test results supported the most likely primary source of neoplasia as being the breast, as well as supported the consideration (and eventual pursuit) of risk-reducing prophylactic surgery.

This case report serves as an example of the importance of considering and offering genetic evaluation and (if appropriate) testing in the presence of single, isolated cases of early onset occult cancer. Identification of a *BRCA* gene mutation in this setting not only allows for the identification of individuals at significantly increased risk for breast and ovarian cancer, but promotes use of that information for informed

medical and surgical management decisions. In addition, it provides the basis for a preventative approach for family members at potential risk.

Acknowledgement

This work was supported by Roswell Park Cancer Institute and National Cancer Institute (NCI) grant #P30 CA016056. At the time this case report was written, Nicoleta Voian, MD, MPH was a Preventative Medicine resident at SUNY at Buffalo School of Medicine and Roswell Park Cancer Institute, in a specialized training track in cancer prevention and control sponsored by the American Cancer Society (PTAPM-02-073-05, Dr. Martin Mahoney, PI).

References

1. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet.* 1998;62(3):676-689.
2. Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival in hereditary breast cancer associated with germline mutations of BRCA2. *J Clin Oncol.* 1999;17(11):3396-3402.
3. Easton D. Cancer risks in BRCA2 mutation carriers: The breast cancer linkage consortium. *J Natl Cancer Inst.* 1999;91(15):1310-1316.
4. Burt RW, Leppert MF, Slattery ML, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. *Gastroenterology.* 2004;127(2):444-451.
5. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. *Lancet.* 1994;343(8899):692-695.
6. Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. *Lancet.* 1998;351(9099):316-321.
7. Frank TS, Manley SA, Olopade OI, et al. Sequence analysis of BRCA1 and BRCA2: Correlation of mutations with family history and ovarian cancer risk. *J Clin Oncol.* 1998;16(7):2417-2425.
8. Abe H, Naitoh H, Ueda T, et al. Occult breast cancer presenting axillary nodal metastasis: A case report. *Jpn J Clin Oncol.* 2000;30(4):185-187.
9. Kyokane T, Akashi-Tanaka S, Matsui T, Fukutomi T. Clinicopathological characteristics of non-palpable breast cancer presenting as axillary mass. *Breast Cancer.* 1995;2(2):105-112.
10. Baron PL, Moore MP, Kinne DW, Candela FC, Osborne MP, Petrek JA. Occult breast cancer presenting with axillary metastases. Updated management. *Arch Surg.* 1990;125(2):210-214.
11. Kemeny MM, Rivera DE, Terz JJ, Benfield JR. Occult primary adenocarcinoma with axillary metastases. *Am J Surg.* 1986;152(1):43-47.
12. Kandel MJ, Stadler Z, Masciari S, et al. Prevalence of BRCA1 mutations in triple negative breast cancer (BC). *J Clin Oncol (Meeting Abstracts).* 2006;24(18 suppl):508.
13. Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. *Histopathology.* 2008;52(1):108-118.
14. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 1989;81(24):1879-1886.
15. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer.* 1994;73(3):643-651.
16. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Statist Med.* 2004;23:1111-1130.
17. Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer.* 2008;98(8):1457-1466.
18. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: Analysis of 10, 000 individuals. *J Clin Oncol.* 2002;20(6):1480-1490
19. Berry DA, Parmigiani G, Sanchez J, Schildkraut J. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst.* 1997;89(3):227-238.
20. Parmigiani G, Berry DA, Aquilar O. Determining carrier probability for breast cancer susceptibility genes BRCA1 and BRCA2. *Am J Hum Gen.* 1998;62(1):145-158.