Salivary Gland Cancer in BRCA-Positive Families
A Retrospective Review

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IMPORTANCE Although an association between breast cancer and salivary gland cancers has been noted for decades, this is the first study, to our knowledge, to evaluate the possible linkage of BRCA gene mutations and this malignant neoplasm.

OBJECTIVE To compare the prevalence of salivary gland cancers in a large BRCA gene mutation database with background rates in the general population.

DESIGN, SETTING, AND PARTICIPANTS This is a retrospective review (June 1, 2012, through April 31, 2013) of pedigrees from patients with breast cancer in The Clinical Cancer Genetics Program at The Ohio State University Wexner Medical Center. A total of 5754 individuals were identified from 187 pedigrees, and their medical histories were reviewed for diagnoses of salivary gland tumors and BRCA testing. The pedigrees were restricted to provide a cohort of individuals with reasonable accuracy in family history by considering 3 generations of each pedigree, starting with the proband's generation and adding 1 generation above and below. The youngest generation was replaced with another older generation if there were no BRCA-related cancers or BRCA mutations recorded. Nonblood relatives of the proband (ie, stepparents and stepsiblings) were also excluded.

MAIN OUTCOMES AND MEASURES The rate of salivary gland cancers in the Clinical Center Genetics Program was compared with background incidence rates.

RESULTS After applying the restrictions to the 187 pedigrees in the database, 5754 individuals were included in the cohort. Two parotid gland cancers, 2 salivary gland cancers not otherwise specified, and 1 adenoid cystic carcinoma were identified. One of these cancers likely did not segregate with the BRCA mutation, and another individual tested negative for the BRCA mutation, resulting in a rate of 3 of 5754 (0.052%). The observed rate of 3 of 5754 cases (0.052%) of head and neck cancers in BRCA-positive probands and likely carriers is significantly higher than the background incidence rate of 3 of 100 000 (0.003%) per year ($P <$ .001).

CONCLUSIONS AND RELEVANCE We believe this is a significant observation that, when considered alongside other similarities between salivary glands and breast tissue, warrants further investigation into the nature of a possible linkage between germline BRCA mutations and salivary gland cancer.

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Research Original Investigation

Methods

The Clinical Cancer Genetics Program at The Ohio State University Wexner Medical Center includes more than 200 BRCA1 and BRCA2 mutation-positive patients with breast cancer and their family pedigrees. This study was approved by The Ohio State University Institutional Review Board and was granted a waiver of consent because of the nature of the research (ie, retrospective medical record review study). In this retrospective review (June 1, 2012, through April 31, 2013), the medical records of 187 pedigrees from individuals enrolled in institutional review board–approved cancer genetics research were searched for diagnoses of salivary gland and parotid gland cancers or other cancers of the head and neck because many of the patients are related and are therefore included in overlapping pedigrees.

The pedigrees were restricted to provide a cohort of individuals with reasonable accuracy in family history and to control for differences in the extensiveness of provided family histories. This restriction was accomplished by considering only 3 generations of each pedigree. Individuals in the 3 youngest generations of each pedigree were first considered. If the youngest generation had no confirmed BRCA mutation testing and no signs of BRCA-related neoplasms, the youngest generation in the pedigree was removed from consideration and the next older generation was added. These generations were removed because they were considered too young for neoplastic manifestations to occur, which could cause a false decrease in the prevalence of cancers in this analysis. Nonblood relatives of the proband (ie, stepparents and stepsiblings) were also excluded because they would not have any genetic association with the proband or the rest of the pedigree.

Results

After applying the restrictions to the 187 pedigrees in the database, we included 5754 individuals in the cohort, including 2636 maternal relatives and 2093 paternal relatives. The remainder of the cohort consisted of 1025 individuals who included the probands, their children, or the proband’s siblings and sibling’s children. Two parotid gland cancers, 2 salivary gland cancers not otherwise specified, and 1 adenoid cystic carcinoma were identified for a prevalence of 5 of 5754 (0.087%) in this population. One of these cancers likely did not segregate with the BRCA mutation, and another individual tested negative for the BRCA mutation, resulting in an observed rate of 3 of 5754 cases (0.052%) of possible BRCA-related salivary gland cancers.

The first identified salivary gland cancer occurred in a paternal uncle in pedigree 1 (Figure 1). Significantly, this was the same side of the pedigree that carried a BRCA2 mutation. However, the individual with salivary gland cancer was never definitively tested for the BRCA2 mutation in the family. The second identified salivary gland cancer occurred in a maternal grandfather in pedigree 2 (Figure 2). Although the maternal...
grandfather was not tested for the family’s BRCA1 mutation, he has a 50% chance of carrying the mutation because his daughter, the proband’s mother, was tested and is a BRCA1 mutation carrier. The salivary gland cancers in these 2 families may be segregating from the BRCA mutation, but this determination has not been directly verified in either case with genetic testing.

The first identified parotid gland cancer occurred in the proband’s mother in pedigree 3 (Figure 3). However, the BRCA mutation in this pedigree was found in the paternal side, not the maternal side. The second identified parotid gland cancer occurred in the proband’s sister in pedigree 4 (Figure 4). This individual was tested and did not carry a BRCA1 mutation. Therefore, one of these parotid gland cancers (from pedigree 3) does not segregate from the BRCA1 mutation. The other parotid gland cancer occurred in an individual known to be negative for the BRCA1 mutation.

Last, the adenoid cystic carcinoma was found in the proband’s mother in pedigree 4. The mother was tested and found to carry the BRCA1 mutation. Overall, from these pedigree reviews, we identified 5 salivary gland cancers in 5754 individuals in BRCA mutation–positive families, 1 of which was identified in a known BRCA1 carrier and 2 of which may be segregating from germline BRCA mutations.

Discussion

The possible association between BRCA gene mutations and head and neck cancers is not well established. One study specifically examined 268 patients with benign pleomorphic salivary gland adenomas that were surgically resected in 2 Polish hospitals and found no statistically significant increase in the number of BRCA1 mutations. However, this study was limited in that individuals were only tested for 3 common BRCA1 mutations found in individuals of Polish descent. Most individuals in our study had full sequencing and targeted deletion or duplication testing for BRCA1 and BRCA2. The aim of our study was to use a long-term breast cancer database to consider this question from another angle. By including confirmed BRCA mutation carriers presenting with breast cancers and their close family members, this study examines 5754 individuals. With this considerably larger cohort, we believe this result will contribute significantly to the emerging literature regarding BRCA mutations and a possible linkage to malignant salivary gland cancers.

It is, however, important to keep in mind the limitations of this approach. Although we attempted to analyze the pedigrees in a manner consistent with extant genetics literature, we are still limited by the accuracy of the patients’ family histories with regard to the number of family members included in the pedigree and their specific medical histories. Some diagnoses of salivary cancers may not have been included in the reported family histories, and some cases may be erroneous. Records were also incomplete with regard to histologic descriptions of the identified cancers and the specific location of the adenoid cystic carcinoma found in pedigree 4. We are also limited by the inability to test many of these individuals for BRCA mutations. Last, we attempted to limit the effects of age of presentation by excluding the youngest generations in which no possible BRCA effects had been observed.

Of note, we were initially interested in including only relatives from the side of the pedigrees that carried the BRCA mutations. Such a step would have enabled us to reduce the number of relatives involved, further increasing the proportion of head and neck cancers found in BRCA mutation–carrying individuals. However, the lack of definitive genetic testing in older family members would have limited the meaningfulness of this analysis, and ultimately we decided to retain the
more conservative analysis. As a result, our proportion likely represents a lower rate of salivary gland cancers than actually exists in the BRCA mutation–carrying family members found in this database. It is notable that our study population has a prevalence of head and neck cancers in BRCA mutation–negative individuals (2 of 5754 [0.035%]) that is also elevated above the background incidence rate. It is possible that these individuals, although not carrying known BRCA mutations, may be carrying other low-penetrance gene mutations that increase the risk of these cancers throughout the pedigrees. Because the family histories for these pedigrees were collected without specifically referencing head and neck cancers, it is unlikely that these cancers were overreported.

**Conclusions**

The observed rate of 3 of 5754 cases (0.052%) of head and neck cancers in BRCA mutation–positive probands and likely carriers is significantly higher than the background incidence rate of 3 per 100,000 (0.003%) per year ($P < .001$). This statistical analysis was performed using a 1-sample z test for proportions. This study resulted in a significant observation that we believe, when considered alongside other similarities between salivary glands and breast tissue, warrants further investigation into the nature of a possible linkage between germ-line BRCA mutations and salivary gland cancer.

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REFERENCES