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BRIEF REPORT

The penetrance of ductal carcinoma in situ among BRCA1 and BRCA2 mutation carriers

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Abstract Ductal carcinoma in situ (DCIS) is a precancerous lesion of the female breast and is strongly suspected to be a precursor of invasive breast cancer (IBC). Our goal is the estimation of the age-specific and lifetime penetrances of DCIS among carriers of either a BRCA1 or BRCA2 deleterious mutation. We jointly re-analyze the SEER9 database and a previous study by Claus et al. (JAMA 293:964–969, 2005). Estimation is performed via Bayes theorem after the evaluation of the ratio of age-specific DCIS incidences, and extrapolation to the general population of the study-specific penetrance obtained from Claus et al. From the SEER9 database, we estimate the lifetime risk of DCIS to be 0.98 %, in contrast to value of 12.5 % usually reported for IBC. By extending the result in Claus et al. to the general population, we obtain a lifetime risk for carriers of a deleterious mutation of either BRCA1 or BRCA2 of 6.21 % (95 % CI 6.09–6.33 %). The increase in lifetime risk of DCIS for a BRCA mutation carrier compared to a non-carrier is therefore about six-fold. Our quantification is directly relevant to the identification and genetic counseling of BRCA mutation carriers, and emphasizes the potential importance of including information on diagnoses of DCIS in counseling of individuals who are at familial risk for breast cancer. All these factors can contribute to a more specific and targeted prevention, potentially reducing the impact of IBC among BRCA mutation carriers.

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Introduction

Deleterious germline mutations in the BRCA1 and BRCA2 genes are known to cause an increase in the rate of invasive breast cancer (IBC) [1–7]. More recently [8, 9] they were also found to increase the risk of ductal carcinoma in situ (DCIS). While estimates of absolute risk of IBC in carriers are available [4, 10] and commonly used for counseling carriers, a similar assessment is lacking for DCIS. None of the widely used tools for carrier status prediction in high risk families take DCIS into consideration explicitly [11–13].

To address this question, here we combine information from the SEER registry with a retrospective study [8] that tested DCIS cases for BRCA status, to obtain estimates of the absolute risk for DCIS among BRCA mutation carriers. A strongly increased risk of DCIS among carriers would call for a radical overhaul of genetic counseling algorithms, which would affect women who have DCIS, as well as those whose relatives have DCIS. Thus, our results have direct implications for the efficient identification, genetic counseling and clinical management of carriers of BRCA1 and BRCA2 mutation. In addition, they provide the foundation for improved accuracy in identifying and counseling families with an inherited genetic susceptibility to breast cancer.

Data sources

Our analysis integrates the following sources:

1. The SEER9 incidence registries for Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San

Francisco-Oakland, Seattle–Puget Sound and Utah. We include all cases of IBC and of DCIS from 1973 to 2006 for women aged 11–108, for a total of 467,994 cases of IBC and 36,563 cases of DCIS.

2. The Claus et al. [8] study which estimates BRCA1 and BRCA2 mutation prevalence among women diagnosed with non-invasive carcinoma of the breast. The study population includes 369 cases between 20 and 79 years of age at time of diagnosis, ascertained among Connecticut residents, from September 1994 to March 1998 and identified through the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center, as well as the Connecticut tumor Registry. Consistently with Claus et al. [8], we will consider "deleterious" mutations in the BRCA1/2 to be those which are commonly known to have an association with the disease, not including variants of unknown significance.

The data for this retrospective study have been obtained in two steps. The initial cohort of women with the features described above was drawn from a case–control study population and included 1,068 cases and 999 controls matched by age. Women with a previous history of breast cancer and/or breast biopsy of unknown outcome were excluded. All available participants in the initial study were subsequently recontacted for testing for mutations in BRCA1 and BRCA2 genes. Among these, 369 women with DCIS agreed to be tested and are considered here. An additional 53 cases with lobular carcinoma in situ are not considered in our study.

Statistical methods

From a statistical standpoint, the goal is to determine the age-specific penetrance function for DCIS, that is the conditional probability of a diagnosis of DCIS by age, given a germline deleterious mutation in either the BRCA1 or the BRCA2 gene.

The assumptions and definitions used in the analysis are as follows.

The first concern we need to address is ascertainment. We consider the probability of being included in the Claus study, denoting by $P_{\text{Claus}}(a)$ the probability of being diagnosed with DCIS at age a during the time between March 1994 and September 1998, for Connecticut-resident women aged 20–79. We estimate this probability by subsampling the SEER database to match the exact characteristics of the women participating in study [8].

Next, we denote by $P_{\text{SEER}}(a)$ and $Q_{\text{SEER}}(a)$ the probabilities of being diagnosed with DCIS and IBC, respectively, at age a in the SEER9 population. We estimated these three probabilities directly by empirical yearly counts from the SEER9 database.

For ages 18–99, the curve $Q_{\text{SEER}}(a)$ was multiplied by a constant to obtain an overall lifetime risk for IBC equal to 0.125 [14]. To maintain consistency, we modified $P_{\text{SEER}}(a)$ so to keep fixed he empirical ratio between age-specific risks for IBC and DCIS, or $Q_{\text{SEER}}(a)/P_{\text{SEER}}(a)$.

The resulting estimate for the lifetime risk of DCIS in the general population is 0.0097659. The result of this procedure is shown in Fig. 1.

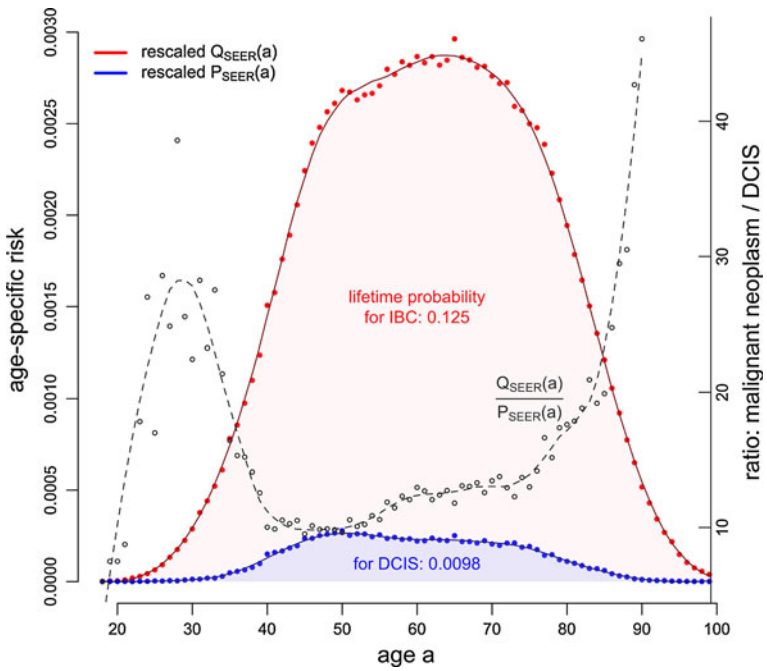

Fig. 1 The curves $Q_{\text{SEER}}(a)$ and $P_{\text{SEER}}(a)$ after rescaling to achieve a lifetime probability of invasive breast cancer equal to the well known value of 0.125 [14]. Consistently, by maintaining fixed the empirical ratio between age-specific risks for IBC and DCIS from the original curves, we are able to obtain the lifetime risk of DCIS in the general population

We use B to denote the presence of a germline mutation in either BRCA1 or BRCA2. We estimated the probability of B as a weighted sum of the combined allele frequencies of the two genes in the Ashkenazy and non-Ashkenazy populations; the weights are the proportions of individuals from Ashkenazy and non-Ashkenazy ancestry in the study [8].

The ratio

$$r(a) = \frac{P_{\mathrm{SEER}}(a)}{P_{\mathrm{Claus}}(a)}, \tag{1}$$

reflects the relative probabilities of inclusions in the two studies at age a, as estimated by the SEER data. We will use it to project the results of the Claus study to the SEER population, by deriving an estimate of the age-specific DCIS penetrance $P_{\mathrm{SEER}}(a|B)$ among carriers as follows:

$$\begin{aligned} P_{\mathrm{SEER}}(a|B) &= \frac{P_{\mathrm{SEER}}(B|a)P_{\mathrm{SEER}}(a)}{P_{\mathrm{SEER}}(B)} \simeq \frac{P_{\mathrm{Claus}}(B|a)}{P_{\mathrm{SEER}}(B)} \\ P_{\mathrm{SEER}}(a) &= \frac{P_{\mathrm{Claus}}(a|B)}{P_{\mathrm{Claus}}(a)} P_{\mathrm{SEER}}(a) = P_{\mathrm{Claus}}(a|B)r(a). \end{aligned} \tag{2}$$

This approximation is based on the assumption that $P_{\mathrm{SEER}}(B|a) \simeq P_{\mathrm{Claus}}(B|a)$, that is that conditional on a diagnosis of DCIS at age a, the proportion of carriers is roughly the same in the two populations.

$P_{\mathrm{Claus}}(a|B)$ was estimated fitting a Gamma distribution to the ages of diagnoses provided in [8] via maximum likelihood, while $P_{\mathrm{SEER}}(a|B)$ was estimated by means of Eq. (2). The curves $P_{\mathrm{Claus}}(a|B)$, $P_{\mathrm{SEER}}(a|B)$ and $r(a)$, as well as the empirical data used to estimate them, are shown in Fig. 2.

Results

We estimate the lifetime risk of DCIS among carriers of BRCA1 or BRCA2 mutations to be 6.21 % (95 % bootstrap CI 6.09–6.33 %). Thus the increase in lifetime risk for a carrier appears to be about six-fold overall.

Figure 3 displays the age-specific curves describing the number of new cases of DCIS occurring in a cohort of carriers followed from birth.

At age 40, this ratio is 11.45 while at age 50 it is 7.63, providing a strong indication of a possible mutation. While the mode of the age distributions of DCIS diagnoses appears to be comparable for carriers and others, we notice a shift towards younger ages of diagnoses among carriers when the entire distribution is considered (median age for the general population equal to 59, bootstrap average

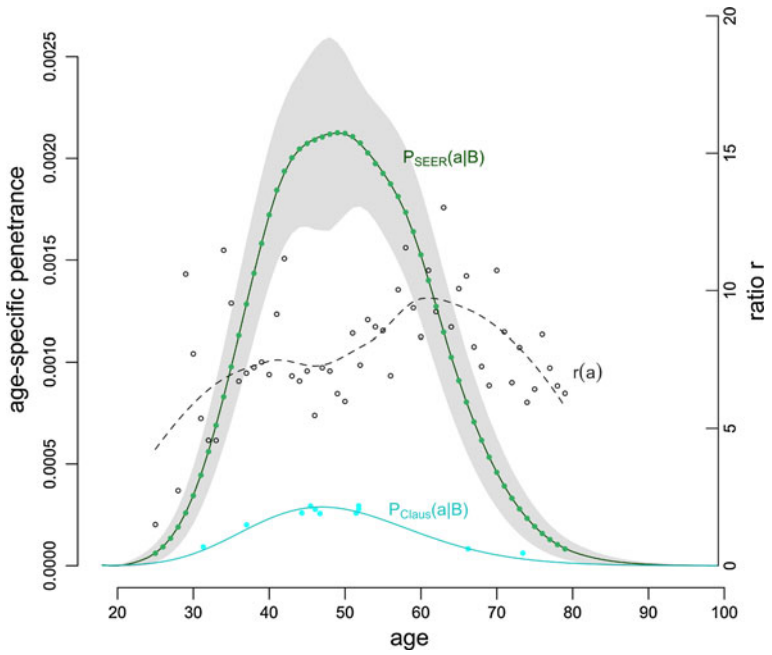

Fig. 2 The curves $P_{\mathrm{Claus}}(a|B)$, $r(a)$ and $P_{\mathrm{SEER}}(a|B)$ and the data used to estimate them. $P_{\mathrm{Claus}}(a|B)$ is the age-specific penetrance of DCIS for mutation carriers estimated from the data in Claus study [8]. The points in the *same color* are positioned at the ages for the cases, and their *height* corresponds to the frequencies obtained estimating the parameters of a gamma distribution via maximum-likelihood method; the *interpolating curve* is the complete estimated density. The curve $P_{\mathrm{SEER}}(a|B)$ is the estimated age-specific penetrance for DCIS in the carrier population. The areas under the *solid lines* are equal to 0.0079 and 0.0621. They represent, respectively, the estimates of the lifetime risk of being diagnosed with DCIS for a woman participating in study [8] and the lifetime risk for the carrier population overall. The *gray-shaded* area is the 95 % bootstrap confidence interval for the age-specific penetrance for the carrier population. Also graphed are curve $r(a)$ and the SEER-based empirical ratios used to estimate it

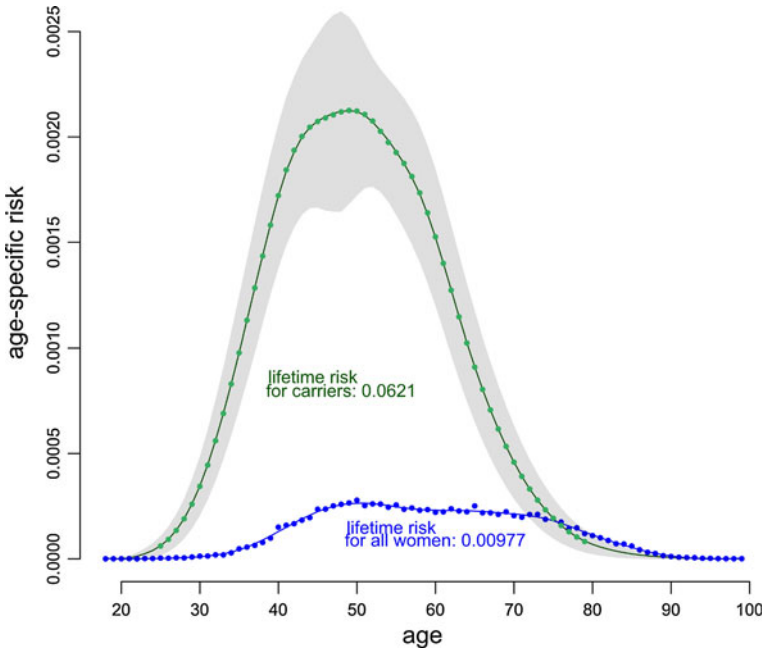

Fig. 3 The curves $P_{SEER}(a)$, or the age specific risk for DCIS in the general population, and $P_{SEER}(a|B)$ or the age-specific risk for carriers of a BRCA mutation in the general population. The *gray-shaded* area is the 95 % bootstrap confidence interval for the age-specific penetrance for the carrier population

median age for the mutation carriers equal to 46 (95 % CI 45–51))

Our quantification is directly relevant to the clinical management of BRCA mutation carriers, and emphasizes the potential importance of including information on diagnoses of DCIS in counseling of individuals who are at familial risk for breast cancer. Moreover, this result can also be the epidemiological basis for expanding existing risk assessment models such as BRCAPRO [11, 15] to account for DCIS. All these factors can contribute to a more specific and targeted prevention, potentially reducing the impact of IBC among BRCA mutation carriers.

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Conflict of interest The authors declare that they have no conflict of interest.

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