Age of onset in familial breast cancer as background data for medical surveillance

A Brandt,1, J Lorenzo Bermejo2, J Sundquist4 and K Hemminki1,3
1Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), 69120 Heidelberg, Germany; 2Institute of Medical Biometry and Informatics, University Hospital Heidelberg, 69120 Heidelberg, Germany; 3Center for Primary Care Research, Lund University, 205 02 Malmö, Sweden; 4Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California 94305, USA

BACKGROUND: Familial breast cancers are known to be of early onset. This article provides differences in the age of onset of breast cancer and death by breast cancer between women with and without a family history.

METHODS: The Swedish Family-Cancer Database was used to estimate the cumulative risk of breast cancer and death by breast cancer according to family history with a stratified Cox model. Family history was defined separately for affected mother or sister considering their diagnostic ages.

RESULTS: The age to reach the same cumulative incidence as women without family history decreased with decreasing diagnostic age of the affected relative. Women with a maternal history reached the risk of women lacking a family history at the age of 50 years between 12.3 (mother affected < 40 years) and 3.3 years (mother affected > 82 years) earlier. The trend for breast cancer mortality was essentially similar.

CONCLUSIONS: Women with mother or sister affected by breast cancer are diagnosed and die at earlier ages than do women without family history. The differences depend on the diagnostic age of the affected relative. The present data may provide a rationale to derive recommendations for the starting age of screening in women with affected family members.

Keywords: breast cancer; familial breast cancer; age of onset; screening recommendations; cumulative risk

A family history of female breast cancer is associated with an increase in the risk of breast cancer in first-degree female relatives by about two-fold, but the magnitude of risk depends on a number of factors, such as diagnostic age (Collaborative Group on Hormonal Factors in Breast Cancer, 2001; Hemminki et al, 2008b). Familial risk has been included in clinical risk estimation models for breast cancer (Gail et al, 1989; Claus et al, 1994; Tyrer et al, 2004), but the manner in which it could be translated into recommendations for a surveillance strategy for at-risk women requires scientific justification (Smith et al, 2004, 2006; Saslow et al, 2007). The guidelines for breast cancer screening of average-risk individuals were based on trials investigating mortality reduction by cancer screening, and the starting age was determined by the onset of breast cancer incidence (IARC, 2002). Although familial breast cancers are known to be of early onset (Claus et al, 1990; Collaborative Group on Hormonal Factors in Breast Cancer, 2001; Hemminki et al, 2008b), data have not been accurate enough to provide a scientific basis for the existing recommendations for the time of implementation of screening methods (Smith et al, 2004). The recommendations for at-risk women emphasise breast cancer diagnosis in relatives before the age of 50 years, thereby leaving open the question about breast cancer in older women.

The aim of this study was to assess (1) the cumulative incidence and risk of death from breast cancer in women with a family history of breast cancer compared with those without a family history of breast cancer and (2) the impact of the relative’s age at diagnosis on the diagnostic age. We used the nation-wide Swedish Family-Cancer Database to estimate the cumulative incidence of breast cancer and the cumulative risk of death by breast cancer in women with a family history of breast cancer, compared with those lacking a family history. Family history was defined separately for an affected mother or sister considering their diagnostic ages. The results may encourage appropriate future analysis to derive recommendations for the starting time of screening in women with an affected family member.

MATERIALS AND METHODS

The Swedish Family-Cancer Database was created in the 1990s by linking information from the Multigeneration Register, national censuses, Swedish Cancer Registry and death notifications (Hemminki et al, 2001). Data on family relationships were obtained from the Multigeneration Register, in which all individuals born in or after 1932 are registered with their biological parents as families; in addition, data on immigrants were included. Thus, the individuals in the Database can be divided into offspring generation (individuals born in or after 1932) and
Table 1  Number and median age of women in the whole study population, women diagnosed with breast cancer and women died from breast cancer according to family history

| Family history | Study population | Women diagnosed with breast cancer | Women died from breast cancer |
|----------------|------------------|------------------------------------|------------------------------|
|                | No.              | Median age at censoring or diagnosis (years) | No. | Median age at diagnosis (years) | No. | Median age at death (years) |
| No family history | 3,480,260        | 32                                  | 36,835 | 51                              | 4,793 | 53                      |
| Mother affected |                  |                                     |                                  |                                  |                                  |
| 0–39 years     | 120,108          | 46                                  | 36,49 | 50                              | 452  | 51                      |
| 40–49 years    | 64,28            | 27                                  | 88    | 39                              | 20   | 42                      |
| 50–59 years    | 23,168           | 34                                  | 381   | 45                              | 42   | 47                      |
| 60–72 years    | 31,728           | 40                                  | 715   | 48                              | 81   | 49                      |
| 73–82 years    | 37,029           | 49                                  | 1,316 | 50                              | 164  | 52                      |
| >82 years      | 16,360           | 57                                  | 829   | 51                              | 109  | 53                      |
| Sister affected |                  |                                     |                                  |                                  |                                  |
| 0–39 years     | 3,100            | 57                                  | 1,780 | 52                              | 228  | 52                      |
| 40–49 years    | 3,331            | 48                                  | 140   | 46                              | 23   | 43                      |
| 50–59 years    | 10,228           | 54                                  | 534   | 51                              | 71   | 51                      |
| 60–72 years    | 12,138           | 58                                  | 760   | 52                              | 99   | 53                      |
| >82 years      | 5,303            | 61                                  | 346   | 54                              | 35   | 56                      |
| Sister+mother affected | 2,794   | 56                                  | 252   | 49                              | 27   | 53                      |
| Two sisters affected | 925     | 58                                  | 76    | 51                              | 12   | 55                      |
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Lacking a family history at the age of 40 and 50 years for death from breast cancer, at which women with a family history reach the cumulative risk of women lacking a family history at the age of 40 and 50 years for incidence. (British Journal of Cancer (2010) 9.5 years when the mother was diagnosed at an age below 40 years according to the diagnostic age of the affected family member. The age difference for sisters decreased from 9.4 years (sister diagnosed before the age of 40 years) to 4.4 years (sister diagnosed between 60 and 72 years). Fatal events were too few for a detailed analysis.

Women with an affected mother and sister, and women with more than one affected sister were considered separately (data not shown). The numbers of women affected by breast cancer in these groups were small. For women with a mother and a sister affected, the age to reach the same risk as the general population at the age of 50 and 40 years were 41.3 years (33 cases until this age, 95% confidence interval (CI): 39.2–43.1 years) and 32.8 years (7 cases, 95% CI: 31.4–36.3 years), respectively. The corresponding ages were 42.3 years (11 cases, 95% CI: 33.4–44.9 years) and 25.8 years (2 cases, 95% CI: 23.3–38.1 years), respectively. The numbers of deaths in women with a mother and a sister affected (27) or with two affected sisters (12) were too small for a separate analysis.

DISCUSSION

Our results provide initial data on the age of onset of familial breast cancer estimated with a large population-based data set. For example, if the general starting age of mammography screening is defined to be 50 years, our data show that the same cumulative risk is reached 9–12 years earlier for women with a mother or a sister affected by breast cancer before 40 years. According to previous recommendations, an earlier start of screening is not recommended for women with mother or sister who was affected older than 50 years. However, the present results indicated that these women are at an increased risk. The estimation of the age at which familial cases reached the risk of death in women without a family history permitted essentially identical conclusions, even though the results were based on a smaller numbers of events.

The American Cancer Society recommends average-risk women begin mammography screening at the age of 40 years (Smith et al., 2007). In the European Union, the Advisory Committee on Cancer Prevention recommends the introduction of organised mammography screening beginning at 50 years (Advisory Committee on Cancer Prevention, 2000). In most nationally organised programmes in Europe and Canada, the starting age of mammography screening is 50 years (IARC, 2002). These screening programmes do not take the family history of breast cancer into consideration, although some guidelines recommend individual strategies when risk factors are present (Albert and Schulz, 2004). The National Board of Health and Welfare recommends Swedish counties to offer mammography screening for women at the age of 40–74 years. There are differences between counties when they start screening and the screening interval (Olsson et al., 2000). The American Cancer Society recommends MRI (magnetic resonance imaging) screening as an adjunct to mammography screening for women with an estimated 20–25% or greater lifetime risk of breast cancer (Saslow et al., 2007). However, the starting age of screening for breast cancer in women at increased risk is not well established. The National Center for Clinical Excellence in the United Kingdom recommends annual mammography screening for at-risk women beginning at the age of 40 years, which is 10 years earlier than the recommended starting age in the United Kingdom for the general population (McIntosh et al., 2004); the increased risk is defined as an estimated lifetime risk of breast cancer between 17–30%, which includes women with a first-degree relative affected by breast cancer before 50 years and women with two affected first- or second-degree relatives (McIntosh et al., 2004). The American Cancer Society recommends women with a relative affected by breast cancer before 50 years, with two or more relatives affected by breast cancer and with a relative affected by two independent breast cancers to start 10 years earlier than average-risk women, or
The rationale of mammography screening is the reduction of mortality by breast cancer. As evidence of an impact of family history on the survival of breast cancer patients in general is lacking (Chappuis et al., 1999; Hemminki et al., 2008a), the cumulative risk of death by familial breast cancer is increased because of the increased incidence. The difference in the age of onset of familial cases might be influenced by overdiagnosis or an earlier detection of familial cases because of increased surveillance of familial cases: women with a close relative affected by breast cancer may participate in cancer screening more often, more frequently or earlier than women in the general population (Shah et al., 2007). The likelihood of lead-time bias motivated us to investigate the difference in breast-cancer-specific mortality between women with and without affected relatives. The present data showed essentially the same differences in age of diagnosis and age of death between women with and without affected relatives. Thus, lead-time bias does not seem to influence the difference in the onset age of breast cancer in familial and non-familial cases. This is in agreement with earlier results that showed at most a minor influence of screening (Bermejo and Hemminki, 2005; Hemminki and Bermejo, 2005).

This study includes the whole Swedish population up to the age of 72 years and their parents. The information on cancer and diagnostic ages was registered data. Thus, an important advantage was the accuracy and completeness of the analysed data, which minimised biases related to over- and under-reporting of family history, selection and recall. The existing recommendations for surveillance of women at increased risk are mainly based on expert opinion, with support from the assessment of breast cancer risk with statistical models (Gail et al., 1989; Claus et al., 1994; Tyrer et al., 2004) or epidemiological studies (Smith et al., 2003; McIntosh et al., 2004). Different models for the prediction of breast cancer risk have been developed. These models include different combinations of risk factors. In the past, the most widely used models were the Gail model and the Claus model (Gail et al., 1989; Claus et al., 1994). The Gail model takes the number of affected first-degree relatives, age at menarche, age at first birth and the number of breast biopsies into account (Gail et al., 1989). This model does not consider the age at diagnosis and includes only first-degree relatives (Evans and Howell, 2007). The Claus model predicts lifetime risk of breast cancer for different combinations of affected first- and second-degree relatives (Claus et al., 1994). However, it does not include risk factors other than family history and it reflects the risk of breast cancer for women in the United States in the 1980s (Evans and Howell, 2007). The BRCAPRO model predicts breast cancer risk on the basis of the probability of carrying a mutation in BRCA1/2, taking cancer status and age of first- and second-degree relatives into account (Parmigiani et al., 1998). This model includes only BRCA1/2 as genetic elements (Evans and Howell, 2007). The Breast and Ovarian Analysis of

### Table 2

| Diagnostic age of relative (years) | Maternal history | Sororal history |
|-----------------------------------|------------------|-----------------|
|                                   | No. | Age (years) | 95% CI | AD | No. | Age (years) | 95% CI | AD |
| First breast cancer               |     |             |        |    |     |             |        |    |
| 0–39                              | 36  | 37.7        | 36.9   | 40.0 | −12.3 | 38  | 41.1        | 38.4   | 43.5 | −8.9 |
| 40–49                             | 158 | 43.3        | 42.2   | 44.2 | −6.7  | 126 | 44.5        | 43.6   | 45.7 | −5.5 |
| 50–59                             | 264 | 44.7        | 43.8   | 45.6 | −5.3  | 146 | 44.8        | 44.1   | 46.1 | −5.2 |
| 60–72                             | 429 | 46.0        | 45.4   | 46.8 | −4.0  | 62  | 47.0        | 45.6   | 48.9 | −3.0 |
| 73–82                             | 214 | 46.1        | 45.2   | 46.9 | −3.9  |     |             |        |    |     |
| >82                               | 66  | 46.7        | 45.3   | 48.0 | −3.3  |     |             |        |    |     |

### Table 3

| Diagnostic age of relative (years) | Maternal history | Sororal history |
|-----------------------------------|------------------|-----------------|
|                                   | No. | Age (years) | 95% CI | AD | No. | Age (years) | 95% CI | AD |
| 0–39                              | 10  | 30.5        | 28.2   | 33.5 | −9.5  | 8   | 33.0        | 28.4   | 35.1 | −7.0 |
| 40–49                             | 45  | 33.7        | 33.1   | 35.1 | −6.3  | 24  | 35.2        | 33.6   | 37.7 | −4.8 |
| 50–59                             | 75  | 35.4        | 34.2   | 36.8 | −4.6  | 28  | 38.1        | 36.5   | 39.0 | −1.9 |
| 60–72                             | 97  | 37.3        | 36.4   | 38.1 | −2.8  | 11  | 39.1        | 37.1   | 41.8 | −0.9 |
| 73–82                             | 41  | 38.6        | 36.5   | 40.1 | −1.4  |     |             |        |    |     |
| >82                               | 12  | 39.3        | 35.3   | 41.2 | −0.8  |     |             |        |    |     |

Abbreviations: AD = age difference; CI = confidence interval. *Number of cases until (Age). **Age to reach the same cumulative risk as women lacking a family history at age 50. 

**Table 2** Age at which women with a family history reach the cumulative risk of women lacking a family history at age 50 years for incidence (top) and for death (bottom) considering the diagnostic age of the relative.

**Table 3** Age at which women with a family history reach the cumulative risk of women lacking a family history at age 40 years for incidence considering the diagnostic age of the relative.
Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model includes a polygenic component for breast cancer susceptibility in addition to BRCA1/2 (Antoniou et al., 2004). The Tyrer–Cuzick model combines the prediction of genetic risk based on family history information and personal risk factors (Tyrer et al., 2004). This study presents empirical risk estimates on the age of onset based on breast cancers in first-degree relatives taking the relative’s diagnosis age into account. Second-degree relatives were not considered because the structure of the Swedish Family-Cancer Database implies that identification of grandparents and aunts is only possible for women whose parents were born in 1932 or later, that is, for women who were aged ~50 years or less at the end of the study.

The efficacy of screening is not equivalent to case detection. There is ample evidence that the efficacy of mammography screening in average-risk women is lower in women aged 40–49 years than in those aged 50–69 years (IARC, 2002; Moss et al., 2006). No evidence has been found for the efficacy of screening under the age of 40 years. However, it has been shown that women with an increased genetic risk of breast cancer might benefit from an intensified surveillance, which includes an earlier start of mammography screening, expert clinical breast examination and teaching of ‘breast awareness’ (Moller et al., 1999). Further research is required to clarify the efficacy of breast cancer screening before 50 and 40 years in women at increased risk of breast cancer.

We conclude that women with mothers or sisters affected by breast cancer were diagnosed at earlier ages than were individuals without a family history. The differences in age of onset depended on the age of affected relatives, whereas the type of proband (mother or sister) seemed to have a minor function. Under the discussed limitations, the present data should encourage further analysis in order to derive evidence-based recommendations for the starting age of screening in women with a family history of breast cancer.

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Conflict of interest

The authors declare no conflict of interest.

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