Evidence-Based Information Retrieval and Evaluation

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Definition
Evidence-Based Medicine

- Abbreviated EBM

- “the conscientious, explicit and judicious use of current best evidence in making decisions about the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett D, BMJ, 1996)
Definition
Evidence-Based Practice

- Abbreviated EBP

- “the formulation of treatment decisions by using the best available research and integrating this evidence with the practitioner’s skill and experience”

  (Stedman’s Dictionary for the Health Professions and Nursing, 2012)
Steps in the Evidence-Based Practice Process

- A clinical problem arises
- Develop the clinical question
- Select appropriate resources**
- Evaluate the evidence**
- Integrate and apply the evidence
- Evaluate your performance with the patient

**Where the library and research skills come into the picture
Definitions

RCTs & Practice Guidelines

- **Randomized Control Trial (RCT)** — study in which a group of clients are randomly allocated into either
  - an experimental group
  - a control group

- **Practice Guideline** — a description of a process of patient care management that facilitates the improvement or maintenance of health status

  - Purpose is to:
    - Identify preferred treatment
    - Describe treatment alternatives

  - Published by subspecialty or disease-specific experts from authoritative national & international societies & organizations, e.g., American Heart Association (AHA), American Academy of Pediatrics (AAP)

  - Not all based on experimental studies
Definition

Review Article (narrative)

- Also called a *narrative review*
- In the health and medical literature, this type of article refers to an article which comprehensively scrutinizes a topic over a period of time
- Provides a broad overview of a topic
- The studies included are selected through an *implicit* process
- May include practical, real-life clinical experiences
- Frequently contains a long list of references in the bibliography
Definition
Systematic Review

- Summarize large bodies of evidence
- Help to explain differences among studies on the same question
- Apply scientific strategies that limit bias to the selection, critical appraisal and synthesis of all pertinent studies that address a specific clinical question (Cook, Mulrow, Haynes, 1997)

In a systematic review:

- Studies are selected through an explicit process
- Methods of the studies are appraised
- Results are summarized
- Key finding presented
- Limitations of the current knowledge-base on a specific topic are acknowledged
Differences Between Narrative and a Systematic Reviews

**Narrative Review**

- **Clinical Question** - seldom reported, or addresses several general questions
- **Search for Primary Articles** – seldom reported; if reported, not comprehensive
- **Selection of Primary Articles** – seldom reported; if reported, often biased sample of studies
- **Evaluation of Quality of Primary Articles** – seldom reported; if reported, not usually systematic
- **Summary of Results of Primary Studies** - usually qualitative nonsystematic summary

**Systematic Review**

- **Clinical Question** - focused question specifying population, intervention, and outcome
- **Search for Primary Articles** – comprehensive search of several evidence sources
- **Selection of Primary Articles** – explicit inclusion and exclusion criteria for primary studies
- **Evaluation of Quality of Primary Articles** – methodologic quality of primary articles is addressed
- **Summary of Results of Primary Studies** - synthesis is systematic (if quantitative, often referred to as meta analysis)

From: *User's Guide to the Medical Literature, 2nd, 2008, p. 525, Guyatt, Rennie, Meade, Cook*
Definition

Integrative Review

- Summarizes past experimental & non-experimental research in order to provide a comprehensive understanding of a problem or phenomenon

- Allows for varied perspectives to be represented

- The body of literature includes all studies that address related or identical hypotheses

- Present the state of science, contribute to theory development, & apply to practice and policy

- May be tagged as systematic reviews (CINAHL) or Reviews (PubMed)
Definitions

Meta-Analysis & Meta-Synthesis

- **Meta-Analysis** - a type of systematic review that uses statistical methods to combine and summarize the results of several primary studies
  
(Cook, Mulrow, Haynes, 1997)

- **Meta-Synthesis** – assembles qualitative data to form a new interpretation of the research topic
  
  Sometimes called a *qualitative systematic review*
Medical Research Library of Brooklyn
Pyramid of EPB Resources

Adaptation of the Evidence Pyramid Diagram developed by the Medical Research Library of Brooklyn, SUNY Downstate Medical Center
Levels of Research Evidence

- **Level I**: Systematic reviews (e.g., Cochrane reviews)
  - Meta-analysis of all relevant randomized clinical trials (RCTs)
  - Evidence-based clinical practice guidelines based on systematic reviews of RCTs
  - Three or more RCTs of good quality that have similar results

- **Level II**: One or two well-designed RCTs

- **Level III**: One or more well-designed controlled trials without randomization

- **Level IV**: One or more well-designed case control or cohort studies

- **Level V**: Systematic reviews of descriptive and qualitative studies (meta-synthesis)

- **Level VI**: Single descriptive or qualitative study

- **Level VII**: Opinions of authorities and/or reports of expert committees

*Additions by E.R. Bucciarelli, 2015

Types of Research Information

- Primary Sources
  - Primary research articles report new findings & conclusions
- Secondary Sources
- Tertiary Sources
Recognizing a Research Article

Most research articles have the following sections:
- Abstract
- Introduction/Background
- Purpose of study
- Review of the Literature
- Methods
- Data Analysis
- Discussion
- Limits of the Study
- Suggestions for further research
- Conclusion
- References
THE identification of the breast-cancer-susceptibility genes BRCA1 and BRCA2 evoked widespread interest in genetic testing among women at risk for a mutation in these genes. We found that 57 percent of women without breast cancer who had a 50 percent chance of carrying a BRCA1 or BRCA2 mutation requested genetic testing. This result indicates the need to determine the efficacy of the various options for reducing the risk of breast cancer and for early detection in women with a BRCA1 or BRCA2 mutation.

Women with a BRCA1 or BRCA2 mutation have a cumulative lifetime risk of invasive breast cancer (up to the age of 70 years) of 55 to 85 percent and of invasive epithelial ovarian cancer of 15 to 65 percent. In these women, the risk of breast cancer begins to increase near the age of 25 years, and their overall survival once breast cancer does develop is similar to that of age-matched patients with sporadic cases of breast cancer; in both, the 10-year survival rate is about 50 percent.

Current risk-reduction strategies for women with a BRCA1 or BRCA2 mutation include regular surveillance, prophylactic mastectomy, oophorectomy, or both; and chemoprevention. In our experience, 50 percent of women who have a BRCA1 or BRCA2 mutation have chosen to undergo prophylactic bilateral mastectomy. Until now, however, there have been only retrospective studies of the efficacy of the procedure in women with an increased risk of breast cancer.
METHODS

Study Subjects

Beginning on January 1, 1992, we studied all women with a BRCA1 or BRCA2 mutation who were being monitored for breast cancer at the Memorial Sloan-Kettering Cancer Center or at participating cancer centers. The data were collected in the Netherlands, where all women had been studied for at least 10 years. Women with a BRCA1 or BRCA2 mutation who were diagnosed with breast cancer before January 1, 1992, and who had a BRCA1 or BRCA2 mutation in whom breast cancer developed before January 1, 1992, and who were diagnosed with breast cancer during the follow-up period (March 1, 2001), were included in the study. In addition, women who were monitored for alternative cancer sites were included if they were diagnosed with breast cancer before January 1, 1992, and had a follow-up period of at least 10 years.

Data Collection and Follow-up

Information on vital status and the occurrence of cancer was extracted from the women's medical files. All women were regularly monitored at the clinic until March 1, 2001, and were enrolled in a longitudinal follow-up program approved by the Institutional Review Board. The protocol was modified in 1995 to include data on the BRCA1 and BRCA2 mutations.

Results

Information on vital status and the occurrence of cancer was extracted from the women's medical files. All women were regularly monitored at the clinic until March 1, 2001, and were enrolled in a longitudinal follow-up program approved by the Institutional Review Board. The protocol was modified in 1995 to include data on the BRCA1 and BRCA2 mutations.

Table 1. Characteristics of the Women.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mastectomy Group</th>
<th>Surveillance Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry</td>
<td>19.7 (7.7)</td>
<td>19.5 (7.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Median age</td>
<td>59.9</td>
<td>59.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>23-86</td>
<td>19-75</td>
<td></td>
</tr>
<tr>
<td>&lt;50 yr (n, %)</td>
<td>11 (14)</td>
<td>17 (27)</td>
<td></td>
</tr>
<tr>
<td>50-69 yr (n, %)</td>
<td>39 (51)</td>
<td>17 (27)</td>
<td></td>
</tr>
<tr>
<td>&gt;69 yr (n, %)</td>
<td>18 (24)</td>
<td>16 (25)</td>
<td></td>
</tr>
<tr>
<td>No. of cases of breast cancer after study entry</td>
<td>63 (84)</td>
<td>56 (85)</td>
<td>0.19</td>
</tr>
<tr>
<td>No. of cases of breast cancer after study entry</td>
<td>12 (16)</td>
<td>7 (11)</td>
<td></td>
</tr>
</tbody>
</table>

+ *P values are mean ± SE. Percentages are rounded to the nearest whole number.

Analysis of BRCA1 and BRCA2 Mutations and Histologic Examination

DNA analysis was performed according to standard procedures. BRCA1 and BRCA2 linkage analysis was used in 1994 and 1995, respectively, to identify the presence of inherited breast cancer. From 1994 to 2000, we used direct mutation analysis. All BRCA1 and BRCA2 mutations were pathogenic, since they resulted in a premature truncation of the BRCA1 or BRCA2 protein.

Mammographic examination was performed with mammography every six months, and yearly mammography since 1995. Magnetic resonance imaging (MRI) has been an option for women with mammographically very dense breasts.
### Table 2. Characteristics of the Eight Women in the Surveillance Group in Whom Breast Cancer Developed.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Diagnosis (yr)</th>
<th>Mutation</th>
<th>Prior Contr.</th>
<th>Follow-up after Diagnosis (mo)</th>
<th>Current Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>4284delAG in BRCA1</td>
<td>No</td>
<td>15</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>17912-164del1885 in BRCA1 (a 3.8 kb deletion affecting exon 11)</td>
<td>No</td>
<td>41</td>
<td>Died of breast cancer</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>4284delAG in BRCA1</td>
<td>No</td>
<td>18</td>
<td>NED</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>17912-164del1885 in BRCA1 (a 3.8 kb deletion affecting exon 11)</td>
<td>No</td>
<td>31</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>17912-164del1885 in BRCA1 (a 3.8 kb deletion affecting exon 11)</td>
<td>No</td>
<td>97</td>
<td>NED</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>1129delAG in BRCA1</td>
<td>No</td>
<td>25</td>
<td>NED</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>1668delA+G1669 in BRCA1</td>
<td>Yes</td>
<td>14</td>
<td>NED</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>17921-36del1510 in BRCA1 (a 5.3 kb deletion affecting exon 22)</td>
<td>Yes</td>
<td>19</td>
<td>NED</td>
</tr>
</tbody>
</table>

*NED denotes no evidence of disease.

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**BREAST CANCER AFTER PROPHYLACTIC BILATERAL MASTECTOMY IN WOMEN WITH A BRCA1 OR BRCA2 MUTATION**

### Table 3. Characteristics of the Tumors in the Eight Women in the Surveillance Group in Whom Breast Cancer Developed.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumor Size</th>
<th>No. of Positive Nodes/Total No. of Nodes</th>
<th>Histologic Type</th>
<th>ER/PR Status</th>
<th>Nodes in Stage of Surveillance No.</th>
<th>Baseline CT</th>
<th>Clinical Breast Exam</th>
<th>Mammography</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25, 13</td>
<td>1/15</td>
<td>Ductal III</td>
<td>Negative</td>
<td>3</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>2/13</td>
<td>Ductal III</td>
<td>Negative</td>
<td>12</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>0/1 sentinel node</td>
<td>Ductal III</td>
<td>Negative</td>
<td>3</td>
<td>NA</td>
<td>SC</td>
<td>NA</td>
<td>SC</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>0/10</td>
<td>Ductal III</td>
<td>Negative</td>
<td>10</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>0/18</td>
<td>Ductal III</td>
<td>Negative</td>
<td>23</td>
<td>NA</td>
<td>SC</td>
<td>NA</td>
<td>SC</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>0/10</td>
<td>Ductal III</td>
<td>Negative</td>
<td>38</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>0/1 sentinel node</td>
<td>Ductal II</td>
<td>Negative</td>
<td>41</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>SC</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>0/1 sentinel node</td>
<td>Ductal III</td>
<td>Positive</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
<td>SC</td>
<td>SC</td>
</tr>
</tbody>
</table>

*BSE denotes breast self-examination, CBE clinical breast examination, MRI magnetic resonance imaging, SC suspicion of cancer, PB high probability of a benign lesion, ND not done, and NA no abnormalities.
Results

Characteristics of the Women

Table 1 lists the general characteristics of the women who chose prophylactic mastectomy and those who opted for surveillance. Significantly more women in the mastectomy group than in the surveillance group had undergone a premenopausal oophorectomy (44 vs. 24 [58 percent vs. 38 percent], P = 0.03). All gynecologic cancers occurred before the age of 56 years; the two such cases in the mastectomy group were ovarian cancer, stage IC. There were no significant differences between the two groups with respect to age, average duration of follow-up after entry into the study, follow-up after premenopausal oophorectomy, and type of mutation. The 26 distinct mutations — 23 in BRCA1 and 3 in BRCA2 — were distributed in a similar fashion in the two groups. The 139 women were from a total of 70 families; the number of women from each family ranged from 1 to 5.

The mean (±SE) duration of follow-up was 2.9 ± 1.4 years (219 woman-years) in the mastectomy group and 3.0 ± 1.5 years (190 woman-years) in the surveillance group (Table 1). The total number of woman-years of surveillance increased from 190 to 318 when the 128 woman-years of surveillance before prophylactic mastectomy was added.

Incidence of Breast Cancer

After prophylactic mastectomy no case of invasive breast cancer was observed in any of the 76 women during 219 woman-years at risk (Fig. 1). In the surveillance group eight invasive breast cancers were detected during 318 woman-years at risk, for a yearly incidence of 2.5 percent. The ratio of observed cases to expected cases was 1.2 (8 vs. 6.7, 95 percent confidence interval,
Discussion of Results

The actuarial mean five-year incidence of breast cancer in the women in the surveillance group (Fig. 1) was 17 ± 7 percent, but the number of women at risk at five years was only eight. To obtain a more stable estimate with longer periods of follow-up, we calculated cumulative incidence probabilities with the use of an exponential model in which the hazard rate was assumed to be constant. According to this model, the yearly incidence of breast cancer was 2.5 percent and the five-year cumulative incidence was 12 percent (95 percent confidence interval, 6 to 23 percent) (Fig. 1). Disregarding the years of surveillance before prophylactic mastectomy and thus restricting the actuarial analysis to the 63 women in the surveillance group, we estimated that the five-year risk of breast cancer was 24 ± 9 percent.

Cox proportional-hazards analysis showed that mastectomy significantly (P = 0.003) decreased the incidence of breast cancer (hazard ratio, 0.95; 95 percent confidence interval, 0.6 to 1.36). After adjustment for the change in menopausal status, the protective effect of mastectomy remained statistically significant (P = 0.01).

Outcome in the Women With Breast Cancer

None of the eight patients in the surveillance group in whom breast cancer developed had been scheduled to undergo prophylactic mastectomy at the time of the diagnosis. The characteristics of the women and the tumors are described in Tables 2 and 3, respectively. Patients 7 and 8 underwent bilateral oophorectomy 14 and 12 months, respectively, before the diagnosis of breast cancer. Of the eight cancers, four (in Patients 1, 2, 4, and 6) were detected between screening sessions (so-called interval cancers). In these four patients the interval from screening to diagnosis was two to five months. The cancers in the other four patients (Patients 3, 5, 7, and 8) were detected during a screening session. Patient 1 became symptomatic eight weeks after her first clinical breast-cancer screening, the results of which were negative. In four of the eight patients, breast cancer was detected before the molecular diagnosis was made.

Histologic Findings in the Mastectomy Group

Invasive cancer was not detected in any of the specimens obtained at the time of prophylactic mastectomy. One 44-year-old woman with a BRCA1 mutation had lobular carcinoma in situ.

DISCUSSION

In this prospective study we assessed the incidence of breast cancer in 139 women with a BRCA1 or BRCA2 mutation who chose to undergo either prophylactic mastectomy or regular surveillance. Whereas breast cancer developed in 8 of 63 women in the surveillance group, no cases of breast cancer occurred among the 76 women who underwent prophylactic mastectomy. The observed number of breast cancers in the group under surveillance is compatible with the reported incidence of breast cancer in women with a BRCA1 or BRCA2 mutation. 16 As compared with the incidence in the surveillance group, the incidence of breast cancer in the prophylactic-mastectomy group was significantly reduced (P = 0.003), but the mean follow-up of three years calls for a cautious interpretation of our results.

Table 2. Characteristics of the Eight Women in the Surveillance Group in Whom Breast Cancer Developed

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis</th>
<th>Mutation</th>
<th>Receiving Oophorectomy</th>
<th>Follow-up After Diagnosis</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>4286delAG in BRCA1</td>
<td>No</td>
<td>1.5</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>IVS12-6c dél 5885 in BRCA1</td>
<td>No</td>
<td>4.1</td>
<td>Died of breast cancer</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>4286delAG in BRCA1</td>
<td>No</td>
<td>3.9</td>
<td>NED</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>4286delAG in BRCA1</td>
<td>No</td>
<td>3.9</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>IVS12-6c dél 5885 in BRCA1</td>
<td>No</td>
<td>9.7</td>
<td>NED</td>
</tr>
</tbody>
</table>
Conclusions: Women with a BRCA1 or BRCA2 mutation may choose to undergo bilateral oophorectomy before menopause, chemoprevention, or both to reduce the risk of breast cancer. Such interventions may reduce the risk of breast cancer by about 50 percent. However, the use of tamoxifen as a preventive agent has been questioned in view of its long-term side effects.

Prophylactic mastectomy is a highly personal decision. In counseling high-risk women, the protective effect of prophylactic mastectomy must be weighed against possible surgical complications and psychological problems. Up to 30 percent of women who undergo the procedure will have surgical complications, depending on the type of surgery and the length of follow-up.

A long-term study of prophylactic mastectomy reported unanticipated repeated operations in 49 percent of women, but these results may not be applicable to prophylactic mastectomies as they are currently performed. Psychosocial studies of women who had undergone a prophylactic mastectomy did not find that, overall, the procedure had detrimental effects on body image and sexuality.

In conclusion, our data and those of Hartmann et al. indicate that prophylactic bilateral total mastectomy substantially reduces the incidence of breast cancer among women with a BRCA1 or BRCA2 mutation. Nevertheless, longer follow-up and studies of more patients are required to establish the protective effect and determine the long-term complications of this procedure.
References

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REFERENCES


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