Hereditary Cancer Publications: Highlights from 2012

This month’s posting is a summary of selected journal articles from 2012 and their abstracts. These peer-reviewed publications highlight the importance of hereditary cancer risk assessment.


**Bottom line:** The article describes the development of an online decision tool for BRCA1/2 mutation carriers who have not had cancer: [http://brcatool.stanford.edu/](http://brcatool.stanford.edu/). The tool enables shared decision making by comparing modeled cancer rates and survival outcomes based on decisions about selecting breast surveillance or risk-reducing mastectomy, and risk-reducing oophorectomy, at different ages.


**Bottom line:** This retrospective cohort study used self-reported lifetime radiation exposure in 1993 BRCA mutation carriers in three European countries to determine the impact on breast cancer risks. Exposure to any diagnostic radiation before age 30 was associated with an increased risk of breast cancer (HR: 1.90, 95% CI 1.20 to 3.00). Breast cancer risk rose with the cumulative dose of radiation, for a significant 3.84-fold elevated risk in women with a dose over 0.0174 Gy. The authors suggest that these results support the use of non-ionizing radiation (for example, MRI) as the main mode of surveillance in young women with BRCA1/2 mutations.


**Bottom line:** This cross-sectional study evaluated the prevalence of APC and MUTYH (MYH) gene mutations in over 7,000 patients with multiple colorectal adenomas. Prevalence of mutations by adenoma count:

<table>
<thead>
<tr>
<th>Adenoma Count</th>
<th>% with APC mutation</th>
<th>% with biallelic MUTYH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>10-19</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>20-99</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>100-999</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>80</td>
<td>2</td>
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</tbody>
</table>

The authors derived a model to predict the probability of APC and biallelic MUTYH mutations based on number and age of adenomas as well as history of colorectal cancer.
ABSTRACTS


Abstract

PURPOSE:

Women with BRCA1 or BRCA2 (BRCA1/2) mutations must choose between prophylactic surgeries and screening to manage their high risks of breast and ovarian cancer, comparing options in terms of cancer incidence, survival, and quality of life. A clinical decision tool could guide these complex choices.

METHODS:

We built a Monte Carlo model for BRCA1/2 mutation carriers, simulating breast screening with annual mammography plus magnetic resonance imaging (MRI) from ages 25 to 69 years and prophylactic mastectomy (PM) and/or prophylactic oophorectomy (PO) at various ages. Modeled outcomes were cancer incidence, tumor features that shape treatment recommendations, overall survival, and cause-specific mortality. We adapted the model into an online tool to support shared decision making.

RESULTS:

We compared strategies on cancer incidence and survival to age 70 years; for example, PO plus PM at age 25 years optimizes both outcomes (incidence, 4% to 11%; survival, 80% to 83%), whereas PO at age 40 years plus MRI screening offers less effective prevention, yet similar survival (incidence, 36% to 57%; survival, 74% to 80%). To characterize patients' treatment and survivorship experiences, we reported the tumor features and treatments associated with risk-reducing interventions; for example, in most BRCA2 mutation carriers (81%), MRI screening diagnoses stage I, hormone receptor-positive breast cancers, which may not require chemotherapy.

CONCLUSION:

Cancer risk-reducing options for BRCA1/2 mutation carriers vary in their impact on cancer incidence, recommended treatments, quality of life, and survival. To guide decisions informed by multiple health outcomes, we provide an online tool for joint use by patients with their physicians (http://brcatool.stanford.edu).

Comment in

Are we ready for online tools in decision making for BRCA1/2 mutation carriers? [J Clin Oncol. 2012] PMID: 22231042

Abstract

OBJECTIVE:
To estimate the risk of breast cancer associated with diagnostic radiation in carriers of BRCA1/2 mutations.

DESIGN:
Retrospective cohort study (GENE-RAD-RISK).

SETTING:
Three nationwide studies (GENEPSO, EMBRACE, HEBON) in France, United Kingdom, and the Netherlands,

PARTICIPANTS:
1993 female carriers of BRCA1/2 mutations recruited in 2006-09.

MAIN OUTCOME MEASURE:
Risk of breast cancer estimated with a weighted Cox proportional hazards model with a time dependent individually estimated cumulative breast dose, based on nominal estimates of organ dose and frequency of self reported diagnostic procedures. To correct for potential survival bias, the analysis excluded carriers who were diagnosed more than five years before completion of the study questionnaire.

RESULTS:
In carriers of BRCA1/2 mutations any exposure to diagnostic radiation before the age of 30 was associated with an increased risk of breast cancer (hazard ratio 1.90, 95% confidence interval 1.20 to 3.00), with a dose-response pattern. The risks by quarter of estimated cumulative dose <0.0020 Gy, ≥ 0.0020-0.0065 Gy, ≥ 0.0066-0.0173 Gy, and ≥ 0.0174 Gy were 1.63 (0.96 to 2.77), 1.78 (0.88 to 3.58), 1.75 (0.72 to 4.25), and 3.84 (1.67 to 8.79), respectively. Analyses on the different types of diagnostic procedures showed a pattern of increasing risk with increasing number of radiographs before age 20 and before age 30 compared with no exposure. A history of mammography before age 30 was also associated with an increased risk of breast cancer (hazard ratio 1.43, 0.85 to 2.40). Sensitivity analysis showed that this finding was not caused by confounding by indication of family history.

CONCLUSION:
In this large European study among carriers of BRCA1/2 mutations, exposure to diagnostic radiation before age 30 was associated with an increased risk of breast cancer at dose levels considerably lower than those at which increases have been found in other cohorts exposed to radiation. The results of this study support the use of non-ionising radiation imaging techniques (such as magnetic resonance imaging) as the main tool for surveillance in young women with BRCA1/2 mutations.

PMID: 22956590


Abstract

CONTEXT:
Patients with multiple colorectal adenomas may carry germline mutations in the APC or MUTYH genes.

OBJECTIVES:
To determine the prevalence of pathogenic APC and MUTYH mutations in patients with multiple colorectal adenomas who had undergone genetic testing and to compare the prevalence and clinical characteristics of APC and MUTYH mutation carriers.

DESIGN, SETTING, AND PARTICIPANTS:
Cross-sectional study conducted among 8676 individuals who had undergone full gene sequencing and large rearrangement analysis of the APC gene and targeted sequence analysis for the 2 most common MUTYH mutations (Y179C and G396D) between 2004 and 2011. Individuals with either mutation underwent full MUTYH gene sequencing. APC and MUTYH mutation prevalence was evaluated by polyp burden; the clinical characteristics associated with a pathogenic mutation were evaluated using logistic regression analyses.

MAIN OUTCOME MEASURE:
Prevalence of pathogenic mutations in APC and MUTYH genes.

RESULTS:
Colorectal adenomas were reported in 7225 individuals; 1457 with classic polyposis (≥100 adenomas) and 3253 with attenuated polyposis (20-99 adenomas). The prevalence of pathogenic APC and biallelic MUTYH mutations was 95 of 119 (80% [95% CI, 71%-87%]) and 2 of 119 (2% [95% CI, 0.2%-6%]), respectively, among individuals with 1000 or more adenomas, 756 of 1338 (56% [95% CI, 54%-59%]) and 94 of 1338 (7% [95% CI, 6%-8%]) among those with 100 to 999 adenomas, 326 of 3253 (10% [95% CI, 9%-11%]) and 233 of 3253 (7% [95% CI, 6%-8%]) among those with 20 to 99 adenomas, and 50 of 970 (5% [95% CI, 4%-7%]) and 37 of 970 (4% [95% CI, 3%-5%]) among those with 10 to 19 adenomas. Adenoma count was strongly associated with a pathogenic mutation in multivariable analyses.
CONCLUSIONS:
Among patients with multiple colorectal adenomas, pathogenic APC and MUTYH mutation prevalence varied considerably by adenoma count, including within those with a classic polyposis phenotype. APC mutations predominated in patients with classic polyposis, whereas prevalence of APC and MUTYH mutations was similar in attenuated polyposis. These findings require external validation.

Comment in
APC gene testing for familial adenomatosis polyposis. [JAMA. 2012]


Abstract
OBJECTIVE:
Due to the increased lifetime risk of endometrial cancer (EC), guidelines recommend that women with Lynch syndrome (LS) age≥35 undergo annual EC surveillance or prophylactic hysterectomy (PH). The aim of this study was to examine the uptake of these risk-reducing strategies.

METHODS:
The study population included women meeting clinical criteria for genetic evaluation for LS. Data on cancer risk-reducing behaviors were collected from subjects enrolled in two distinct studies: (1) a multicenter cross-sectional study involving completion of a one-time questionnaire, or (2) a single-center longitudinal study in which subjects completed questionnaires before and after undergoing genetic testing. The main outcome was uptake of EC risk-reducing practices.

RESULTS:
In the cross-sectional cohort, 58/77 (75%) women at risk for LS-associated EC reported engaging in EC risk-reduction. Personal history of genetic testing was associated with uptake of EC surveillance or PH (OR 17.1; 95% CI 4.1-70.9). Prior to genetic testing for LS, 26/40 (65%) women in the longitudinal cohort reported engaging in EC risk-reduction. At one-year follow-up, 16/16 (100%) mismatch repair (MMR) gene mutation carriers were adherent to guidelines for EC risk-reduction, 9 (56%) of whom had undergone PH. By three-year follow-up, 11/16 (69%) MMR mutation carriers had undergone PH. Among women with negative or uninformative genetic test results, none underwent PH after testing.

CONCLUSIONS:
Genetic testing for LS is strongly associated with uptake of EC risk-reducing practices. Women found to have LS in this study underwent prophylactic gynecologic surgery at rates comparable to those published for BRCA1/2 mutation carriers.

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PMID: 22940489


Abstract
Women who inherit a mutation in either the BRCA1 or BRCA2 gene have greatly elevated lifetime risks of ovarian cancer, fallopian tube cancer and breast cancer. Preventive surgical removal of the ovaries and fallopian tubes (salpingo-oophorectomy) is recommended to these women, often prior to natural menopause, to prevent cancer. The ensuing hormone deprivation may impact on health and quality of life. Most of these women experience menopausal symptoms shortly after surgery; however, there may also be longer term consequences that are less well understood. In this review, we highlight recent studies that examine the implications of salpingo-oophorectomy on health and quality of life in BRCA-positive women and we discuss the care of women following prophylactic surgery.

PMID: 22934728