Survival Analysis of Cancer Risk Reduction Strategies for *BRCA*1/2 Mutation Carriers

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The term *evidence-based medicine* was first coined by Sackett and colleagues[1] as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program titled "Evidence-Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Inc. and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. A listserve discussion is held where participants can discuss the monthly article. Fellows and candidates of the College can access Evidence Based Reviews in Surgery through the American College of Surgeons website (www.facs.org). All journal articles and reviews are available electronically through the website. Currently we have a library of 50 articles and reviews which can be accessed at any time. Each October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of multiple choice questions. Additional information about EBRS is on the ACS Web site or by email to the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS websites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery* and the other 4 will be published in the *Journal of the American College of Surgeons* each year.

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SELECTED ARTICLE

Survival Analysis of Cancer Risk Reduction Strategies for *BRCA*1/2 Mutation Carriers

Kurian AW, Sigal BM, Plevritis SK. J Clin Oncol 2009;22:1-10

Question: What are the risk-reducing strategies in BRCA1/2 mutation carriers?

Design: Monte Carlo model to stimulate different strategies (annual mammography plus magnetic resonance imaging (MRI); prophylactic mastectomy (PM) and/or prophylactic oophorectomy (PO)) for reducing cancer mortality in BRCA1/2 mutation carriers compared to no intervention.

Base Case: Twenty five year old BRCA1/2 mutation carrier.

Outcomes Considered: Overall survival, breast cancer death, ovarian cancer death, prophylactic mastectomy, and prophylactic oophorectomy.

Results: With no intervention, survival probability by age 70 is 53% for BRCA1 and 71% for BRCA2 mutation

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carriers. The most effective single intervention for *BRCA1* mutation carriers is PO at age 40, yielding a 15% absolute survival gain; for *BRCA2* mutation carriers, the most effective single intervention is PM, yielding a 7% survival gain if performed at age 40 years. The combination of PM and PO at age 40 improves survival more that any single intervention, yielding 24% survival gain for *BRCA1* and 11% for *BRCA2* mutation carriers. PM at age 25 instead of age 40 offers minimal incremental benefit (1% to 2%); substituting screening for PM yields a similarly minimal decrement in survival (2% to 3%).

Conclusions: Although PM at age 25 plus PO at age 40 years maximizes survival probability, substituting mammography plus MRI screening for PM seems to offer minimal decreased survival. These results may guide women with *BRCA1/2* mutations in their choices between prophylactic surgery and breast screening.

Commentary: It is estimated that world wide greater than 1 million women are diagnosed with breast cancer and 200,000 are diagnosed with ovarian cancer annually. Within the past two decades, researchers have identified several specific mutations in the human germline DNA that are associated with inherited susceptibility for cancers of the breast, ovarian, thyroid, colon, stomach and pancreas. The most well known of these high-penetrance mutations are within the BRCA1 and 2 tumor-suppressor genes and are linked to early age onset breast and ovarian cancer. Although only an estimated 0.1% of the general population carry these germline mutations, if present they confer a significant lifetime risk for the development of these or certain cancers. BRCA 1 mutation carriers have an approximate 50-70% lifetime risk of breast cancer and a 20-40% lifetime risk of ovarian cancer with BRCA 2 mutation carriers having slightly lower associated risks. Testing for these mutations requires only a simple blood analysis; however the implications of a positive test on the index patient and their family are marked.

Kurian et al[1], performed a decision analysis to examine survival and causes of death in BRCA1/2 mutation carriers comparing no intervention to the three risk-reducing strategies of mammography plus breast MRI screening with or without prophylactic oophorectomy, or prophylactic mastectomy with prophylactic oophorectomy.

Decision analysis is the appropriate design to answer this question as evidence is scant and accrual to a randomized controlled trial would be difficult due to patient's preferences. As is essential in a decision analysis the author's sources of data and processes are explicitly stated. They appear thoughtful and sensible. Some care must be taken when using these results as the cohort examined consists of 25 year old BRCA1/2 mutation carriers. Women being identified with BRCA1/2 are generally older, the average age being mid 40's, and/or are discovered following a cancer diagnosis[2].

The assumptions used in this model are primarily contemporary and comprehensive. Screening guidelines incorporate the use of breast MRI and mammography is assumed to be less sensitive in younger women due to breast density.

This study appropriately separates the BRCA 1 and 2 mutations carriers into distinct groups with different survival and cause-specific mortality. In both models, they incorporate other causes of mortality including those resulting from premenopausal oophorectomy and also perform well designed sensitivity analyses altering the risks for developing cancers, breast tumor growth rates, sensitivity of MRI and the impact of oral contraceptive use on the development of cancers. The model may have overestimated the efficacy of cancer treatment with adjuvant therapies such as hormonal and chemotherapy. The authors assumed equivalent prognosis to those with sporadic breast cancer; however, the majority of BRCA 1 associated breast cancers are estrogen, progesterone and HER-2/neu negative or "triple negative" and carry a worse prognosis. The model appropriately includes the correct distribution of these receptors by subject age but incorporates dated outcomes for adjuvant therapy from the Early Breast Cancer Trialists group which analyzed survival for primarily hormone receptor positive, early stage breast cancer patients. The authors did not include the use of prevention agents such as Tamoxifen which may be most applicable to the BRCA 2 population and less important for the BRCA 1 subjects. One additional important point regarding the assumptions in the models is the lack of a population in which cancer is identified at the prophylactic surgery. Although these are small in number and cancers would likely be early stage, they would potentially alter the survival and cause specific mortality if present at the early age prophylactic surgeries.

Survival probability and to a lesser extent causes of death were the main outcomes in the study.

The most effective survival strategy was found to be prophylactic oophorectomy at age 25 plus prophylactic mastectomy at age 25. This approach improved survival by age 70 for BRCA1 mutation carriers from 53% with no intervention to 79%, and for BRCA2 mutation carriers, from 71% to 83%. Screening between ages 25 to 40 and delaying prophylactic mastectomy to age 40 in BRCA1/2 carriers resulted in only a 1-2% decrement in survival. Replacing prophylactic mastectomy between ages 25 and 40 with MRI based breast screening in the presence of prophy-

lactic oophorectomy at age 40 yields only a 3 to 5% decrement in survival.

There are some further considerations to the study's primary outcome. Survival outcomes were given as percent alive at 70 years. However, the average length of time gained from a baseline strategy may be a more appropriate metric[3]. Differences in survival between the different strategies are small so perceived quality of life with each strategy would likely be the major determinant of a woman's decision to pursue intensified screening versus risk-reducing surgery. The authors were correct in not including utilities and quality of life outcomes to capture emotional outcomes. An attempt to measure utilities, even from women with the same disorder, would unlikely be of value to a woman faced with this decision. When trying to support individual decision making, the only credible quality of life considerations are those of the patient[4,5]. A good example of where quality of life measures are useful is in the authors' previous publication on the cost-effectiveness of screening MRI in BRCA 1/2 carriers targeted at policy makers[6].

Another clinically important outcome affecting quality of life that women need to consider, available from the paper but not emphasized by the authors, is the differences between strategies in the chance of developing a cancer. This is greatly decreased in the prophylactic surgery group and relatively unchanged in the screened group from the baseline of no intervention.

The summary of the risk reduction for cancer occurrence is clinically useful. Many women choose prophylactic surgery for the absolute risk reduction and benefit of avoiding the entire cancer experience, rather than the actual survival benefit. For those who have lost family members to breast and ovarian cancer this is a particularly important factor in decision making. They simply do not want to go through what their mothers or sisters went through and don't want to put their loved ones through the experience either.

In a decision analysis sensitivity analyses are performed to examine the potential impact of uncertainty of the evidence on the outcomes. Reasonable one-way sensitivity analyses (varying one parameter at a time) were performed in this model on all important parameters including BRCA1/2 mutation penetrance, the growth patterns of BRCA1/2-associated breast cancers and their detectability by screening, the impact of oral contraceptive use on breast and ovarian cancer risk, and the effect of premenopausal prophylactic oophorectomy on breast cancer and other health outcomes. Overall and cause-specific survival changed by up to 22% from the base case; however, none of the factors dramatically affected the ranking of the interventions. The only concern was that survival differences between prophylactic mastectomy and MRI-based breast screening could increase from 3% up to 8% for BRCA1 mutation carriers. This is probably a clinically important difference. Methods for two and three-way analyses exist, but do not appear to be performed in this study. Interestingly, changes in MRI sensitivity ranging from 50% to 90% had only minimal effects on survival ranging from 2% to 3%. Consistent with this finding and in contrast to trends in the use of MRI in clinical practice, a previous study by these authors assessing the cost-effectiveness of MRI screening in addition to mammography in BRCA1/2 patients suggests a more restricted use of this modality[6].

The authors have succeeded in providing survival estimates and causes of death information to assist individual patients to make personalized cancer risk management decisions. In general the evidence supports the conclusion that mammography plus breast MRI screening with prophylactic oophorectomy, provides a similar survival as prophylactic mastectomy with prophylactic oophorectomy. However, the incidence of cancer is relatively unchanged in the MRI screened group as compared to the group with no intervention. A randomized controlled trial of these strategies is not likely to be performed, so this evidence is the best available data to date and likely for many years to inform on the survival and causes of death in BRCA1/2 mutation carriers using the various strategies. Improvements on this excellent resource will come from the authors updating the decision model as new observational evidence becomes available.

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