EDITORIAL

Risks and Benefits of Risk-Reducing Surgery in Inherited Breast and Gastric Cancer Susceptibility

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Prophylactic risk-reducing surgery has been earlier suggested effective to improve survival in individuals selected on the basis of a strong family history. Now, genetic increasing the accuracy of cancer risk estimates allows surgery to target individuals with CDH1 or BRCA1/BRCA2 mutations who are at high risk of developing gastric cancer and breast cancer respectively. Here, we discuss the reinvigorated role of prophylactic surgery in the management of hereditary diffuse gastric cancer (HDGC) and inherited breast cancer syndromes. Conventional surgery in the treatment of solid tumors suggests a recently declining trend. Endoscopic and laparoscopic techniques are increasingly replacing traditional surgery as both rates of early detection and minimally invasive treatment are steadily increasing. Premalignant lesions and early-stage small cancers confined to the mucosal layer along the whole gastrointestinal tract - from esophagus and stomach to the colorectum - can now curatively be resected by minimally invasive techniques substantially improving the quality of life of many patients.

In contrast, traditional surgical resection of specific organs for the protection of individuals at very high risk of developing inherited cancer in the breast, colon, and stomach is increasingly receiving considerable attention. However, although surgery is the only preventive intervention able to eliminate the risk of cancer at a specific organ, surgical prophylaxis has been controversial for a numerous of reasons and questions have been raised. Here we discuss the benefits and obstacles of prophylactic surgery.

Hereditary cancer syndromes are rare. They account for less than 5% of all cases because most breast, colon or gastric adenocarcinomas occur sporadically. These syndromes include hereditary nonpolyposis colon cancer syndrome (HNPCC), Peutz-Jeghers syndrome, Cowden's syndrome, and some kindreds affected with Li-Fraumeni syndrome and familial adenomatous polyposis. Germ-line mutations in BRCA1 and BRCA2 genes have been identified, 8 years ago, to cause hereditary breast-ovarian cancer syndrome. Women with mutations in BRCA1 and BRCA2 genes have a cumulative lifetime risk of 50% to 85% for breast cancer and a 10% to 40% risk of ovarian cancer. Carriers of a mutation in CDH1 gene are thought to have an approximately 70% lifetime risk of gastric cancer; 67% for men and 83% for women who had an additional risk of 39% for breast cancer.

This high risk of breast-ovarian cancer and gastric cancer in carriers of mutations in BRCA and CDH1 genes, the ineffectiveness of surveillance and the high lethality by late diagnosis are the main argues for the recommendation of prophylactic surgery as a reasonable strategy. Several current studies validate this prevention option.

In a recent study of 119 women carrying BRCA mutations, breast cancer at three-year period developed in 8 syndrome caused by germ-line mutations in CDH1, the gene encoding E-cadherin, has been added in the list of these syndromes.

Surgery in the prophylaxis of multiple-cases family members is not an innovative approach. Prophylactic bilateral mastectomy in women with a family history of breast cancer has been previously performed and proposed as effective in reducing the risk of breast cancer. However, this preventive approach has been strongly criticized, particularly because surgery may be nontherapeutic and thus, unnecessarily performed in many women selected on the basis of family history and clinical criteria. By contrast, genetic testing provides a more accurate risk assessment allowing surgery to target individuals who are really at very high risk of cancer. Indeed, estimates indicate that only 25% among members of the families with hereditary breast-ovarian cancer or diffuse gastric cancer syndrome, are carriers of mutations in BRCA and CDH1 genes respectively.

The knowledge of the probability that cancer will in fact develop in a carrier of a particular mutation -the penetrance of the mutation- is essential in the clinical management of these high-risk persons. Women with mutations in BRCA1 and BRCA2 genes have a cumulative lifetime risk of 50% to 85% for breast cancer and a 10% to 40% risk of ovarian cancer. Carriers of a mutation in CDH1 gene are thought to have an approximately 70% lifetime risk of gastric cancer; 67% for men and 83% for women who had an additional risk of 39% for breast cancer.

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of 63 women who had elected close clinical surveillance but in none of the 76 carriers of such mutations who had undergone prophylactic surgery. In two other current and simultaneously published studies, prophylactic oophorectomy was performed in women with BRCA mutations after childbearing was complete, although the risk of ovarian cancer is considerably lower than the risk of breast cancer. In both studies salpingo-oophorectomy, as compared with intense surveillance, reduced significantly not only the risk of BRCA-related gynecologic cancer, but also the risk of breast cancer.

Since the first description in 1998 that inactivation of CDH1, a tumor suppressor gene, in 3 Maori families predisposed to HDGC, the first clinical implications of this discovery confirm the high penetrance of this gene. Microscopic foci of diffuse gastric cancer were found in all 10 gastrectomy specimens of asymptomatic carriers of CDH1 germline mutations in two recent simultaneously published studies. Surveillance with endoscopic biopsies, endoscopic ultrasonography and/or chromoendoscopy was proven ineffective to predict the disease. Although these results support the role of prophylactic surgery in the management of CDH1 mutations carriers, they are limited by the small numbers, lack of follow-up and the unknown natural history and biological behavior of these early lesions.

**Argues against surgical prophylaxis**

Although most authors and experts advocate prophylactic surgery as more effective preventive strategy than closed surveillance for BRCA and CDH1 mutation carriers, there is a number of limitations and questions. None of available studies is randomized trial, the time to cancer rather than overall survival was selected as end point, the penetrance of these genes is incomplete, there is an additional risk of cancer at another organ, and surgery-related adverse effects on morbidity and quality of life may be substantial. Prophylactic bilateral mastectomy had a negative effect on self-esteem, sexual relationships and satisfaction with body appearance. Salpingo-oophorectomy, apart of these psychosocial and sexual effects, may have adverse effects on the lipid profile cardiovascular disease, osteoposteoarthritis and may produce more physical symptoms than those who underwent screening.

Similarly, prophylactic gastrectomy is associated with considerable adverse effects on morbidity and quality of life. Because of the nature of HDGC to affect with multifocal lesions the whole stomach only total gastrectomy is indicated, which however, is associated with more adverse effects on morbidity, nutritional status and quality of than partial resection of the stomach. Although total gastrectomy may potentially cause death and disability the rates of postoperative morbidity and mortality have been recently drastically reduced. Especially for young healthy CDH1 carriers undergoing a prophylactic and thus simple total gastrectomy, without resection of neighbouring organs or node dissection, this risk is minimal. Clinically relevant is the effect of total gastrectomy on quality of life. Postoperative weight loss and other metabolic and nutritional changes are considerable. However, both adequate reconstruction after total gastrectomy and nutritional surveillance decrease the risk of developing severe disturbances in bone metabolisms, food intake, body composition, and quality of life. Although it remains controversial which reconstruction method provides the best quality of life several reports indicate a superiority of jejunal pouch versus Roux-en-Y technique. Because of incomplete penetrance and substantial adverse effects of total gastrectomy on morbidity and quality of life, close surveillance and chemoprevention might be an alternative preventive intervention. Indeed, since in sporadic gastric cancer there is optimism towards development of effective preventive interventions and strong promises are provided by recent chemoprevention studies with Helicobacter pylori treatment and vitamin C supplementation, such a prevention strategy of CDH1 carriers might delay time to gastric cancer appearance. However, at the present time this is clearly a simple our speculation and hypothesis since no related data exist.

A similar limitation also exists for prevention decision in inherited breast cancer. The incomplete penetrance of BRCA mutations, estimated at approximately 70%, is argued against prophylactic surgery, which will be nontherapeutic and unnecessary in the 30% of the carriers. Besides this limitation, carriers of these mutations have an additional cancer risk, although substantially lower, to develop cancer at other organs. This challenges medical decision. Whether risk-reducing surgery, such bilateral mastectomy or salpingo-oophorectomy after childbearing is completed, or surveillance is the ideal prevention strategy is unknown. Risk-reducing surgery offers higher cancer protection than surveillance but it is associated with higher side-effects profile. Surveillance is currently receiving attention and seems an attractive alternative preventive intervention. Indeed, advances in imaging technology including magnetic resonance imaging (MRI) and positron emission tomography (PET) allow an early detection of breast cancer in BRCA1/BRCA2 carriers. This surveillance combined with chemoprevention with the selective estrogen receptor modulators tamoxifen or raloxifen, which have been proven effective in prevention of sporadic breast cancer, provide promises for effective nonsurgical preventive interventions for carriers of BRCA1/BRCA2-mutations.

In summary, genetic testing in high-risk family members is strongly recommended. In unaffected siblings prophylactic surgery should not be considered in the prevention strategy because cancer risk is unknown. Carriers of mutations in BRCA1, BRCA2 or CDH1 genes are at high risk of breast-ovarian cancer or gastric cancer respectively, but the clinical management remains controversial. For medical recommendation according to the evidence-based principles, more prospective data with appropriate surveillance protocol, longer follow-up and overall survival as endpoint are needed. At the present time the available current data indicate the superiority of surgical prophylaxis as compared with surveillance in reducing the risk of cancer in carriers of BRCA or CDH1 mutations. However, all the adverse effects and limitations of surgery should also be discussed in extensive preoperative counselling.
REFERENCES