Aspirin in Prevention of Ovarian Cancer: Are We at the Tipping Point?

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Experimental, epidemiological, and clinical data over the last two decades have supported the hypothesis that aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) possess anticancer properties. Experimental data suggest induction of apoptosis, inhibition of angiogenesis, and enhanced cellular immune responses as possible mechanisms (1). Epidemiological studies have in many cases shown an inverse association between cancer incidence and regular administration of NSAIDs (2), whereas clinical data have demonstrated reduction in the development of cancer precursor lesions as well as cancer incidence and mortality rates after regular administration of such drugs (3,4). Positive effects have been demonstrated most clearly in colorectal cancers, but accumulating data support the hypothesis that benefit is likely for a much broader spectrum of malignancies, including ovarian cancer (5). Increasing interest in the issue led to an international consensus statement published in 2009 in the Lancet, which emphasized the substantial potential for chemoprevention using anti-inflammatory medications while highlighting the need for well-designed clinical trials able to adequately assess risk and benefit and ultimately help define individuals who may benefit from such intervention (6).

Ovarian cancer continues to be the most lethal of all gynecological cancers, largely because of delayed presentation of symptoms, rapidly acquired chemoresistance, and a paucity of newer effective agents. Screening methods have to date proved largely ineffective, and chemoprevention remains a vastly understudied paradigm. Within this context, the Trabert et al. article (7) in this issue of the Journal is a much welcomed addition to published literature investigating possible chemoprevention strategies. This pooled analysis of 12 population based case–control studies creates a large sample size of more than 10,000 case subjects from which robust conclusions may be drawn. The authors have done much to reduce the possibility of confounding factors inevitably present in this form of retrospective analysis and have presented data of a clinically meaningful nature by virtue of the attention paid to dose, duration, and frequency of medication administration, as well as to the histological subtypes of affected individuals. They conclude a beneficial effect resulting from aspirin administration, most strongly observed in women with high-grade serous ovarian cancer using low-dose (<100 mg) aspirin on a daily basis. Similar trending benefit was also seen for nonsteroidal anti-inflammatory medication, but importantly, no benefit was noted for women using acetaminophen. These negative findings add depth to the analyses and act as an important control observation. Additional sensitivity analyses performed did not alter the key findings reported. Clearly both limitations pointed out by the authors, including recall bias and inconsistencies between studies with respect to definitions of frequency and duration of medication administration, remain. These have the potential to introduce data distortion and must be more accurately evaluated in future trials.

Many studies, both retrospective and prospective, investigating a potential role for NSAIDs in the prevention of ovarian cancer have been undertaken. The majority are referred to by Trabert et al. (7), who rightly assert that results have been varied. Although some conclude obvious protective effects to aspirin use, others refute such an association. Several more recent meta-analyses equally draw contradictory conclusions (8,9). Additional studies of this kind seem unlikely to conclusively ascertain the appropriate use, if any, of NSAIDs in the prevention of ovarian cancer. So where do we go from here?

When considering the development of a preventative intervention, risk and benefit analysis becomes paramount. Inherent to any chemoprevention strategy is the fact that a large number of healthy individuals be treated with an agent that must be of very low toxicity, such that an acceptable number of adverse effects will justify the prevention of other adverse effects, in this case ovarian cancer, likely to occur in only a small percentage of those treated. The lifetime incidence of ovarian cancer is only 1.4% to 1.7% (10), such that only an exquisitely effective and safe drug would ever prove appropriate in this setting. However, there exist well-defined, high-risk subpopulations, such as those harboring mutations within the BRCA1 and BRCA2 genes, that have an associated lifetime risk of ovarian cancer that may be as high as 39%. These women not only represent a population more likely to benefit from preventative intervention, they also constitute a cohort more easily evaluated by more pragmatic randomized trials. Just as individuals with familial adenomatous polyposis have become the target of intense research of this kind in the context of colorectal cancer (11), so too must women harboring BRCA mutations. To our knowledge, no such research has been undertaken, and future trials should concentrate on targeting this high-risk population.

Randomized chemoprevention trials in an unselected population present a logistic challenge. They require extremely large sample sizes to afford them statistical power as well as follow-up of several decades. These limitations make them impractical and unpopular. In the case of chemoprevention with the easily available and low-cost aspirin, the impetus for such research must come
from pressure within the scientific community if funding is to be secured for such ventures.

Even in high-risk populations where the lifetime disease incidence is high, annual incidence of disease remains low because the prevalence of BRCA1 or BRCA2 mutations and other predisposing factors is low. In Ontario, Canada, a prevalence study estimated the prevalence of BRCA1 and BRCA2 mutations at 0.32% and 0.69%, respectively. In higher-risk populations, such as women of Ashkenazi Jewish descent or women with both a family history and Ashkenazi Jewish descent, the prevalence increases substantially.

Simple calculations help quantify the potential magnitude of the benefit and are instructive in planning future studies. If the level of benefit seen with aspirin in Trabert et al. (7) is 20%, based on a hazard ratio of 0.8, 295 women would have to be treated with aspirin to prevent one case of ovarian cancer. Alternatively, if the benefit of intervention is 36%, with a hazard ratio of 0.64, treating 164 women would prevent one case of ovarian cancer. Restricted to a defined high-risk population such as women with BRCA1 mutations, the numbers needed to treat to achieve a similar magnitude of benefit fall dramatically to between eight and 13. More detailed calculations accounting for lower lifetime risk associated with BRCA2 mutations, differing prevalence of BRCA1 and BRCA2 mutations in the general population, and age allow a more precise estimate of number needed to treat and sample sizes for potential trials.

Thoughtful design approaches are essential and must include the possibility for well-chosen surrogate endpoints. These should include incorporation of rates of pathologic findings both premalignant and malignant in specimens from women undertaking prophylactic salpingo-oophorectomy.

The article by Trabert et al. (7) highlights the growing body of evidence supporting a possible protective effect of aspirin against ovarian cancer development. It complements key findings showing a protective role for aspirin in preventing cardiovascular disease, colorectal cancer, and other cancers. The mounting evidence now begs the question: When should physicians recommend aspirin as a chemopreventive agent to optimize risk/benefit for patients? In the cardiovascular arena, aspirin is recommended when high-risk individuals are identified. For colorectal cancer, prevention is considered for patients with polyposis coli. For ovarian cancer, we now need to mount key epidemiological studies that will address this question for defined high-risk patients (with germline BRCA mutations and strong family histories) as well as the risk/benefit in women not defined to be at high risk.

Are we at the tipping point to initiate these trials? We believe so.

References


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