Editorial

Cancer Prevention: The Importance of Accurate Risk Assessment

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We are now at the beginning of an important era in the clinical application of cancer prevention research. Research over the last 20 years has identified strategies for the prevention of many common cancers, and we are now in position to intervene to reduce the incidence of these cancers using dietary, behavioral, or medical interventions. However, some of these interventions are associated with risk of significant unwanted effects. Thus, a major challenge now is to identify individuals who will most benefit from these preventive interventions, and minimize the number of people who will be needlessly exposed to the potential toxicities of such interventions.

Cancer Prevention: Population Based or Individualized?

Traditionally, the practice of cancer prevention has been viewed as a general public health effort, similar to the prevention of infectious diseases such as polio or small pox. According to this paradigm, cancer prevention interventions should be delivered to the general population to completely eradicate the disease. Although this is certainly a laudable goal, total eradication of cancer has not been possible to date. In addition, such a global strategy may not be possible given the many different types of cancer, the myriad causes of cancer, and the potential toxicity of preventive strategies. The practice of applying cancer preventive interventions to the general population would be feasible only if the intervention was extremely safe, well tolerated, and acceptable to most healthy individuals. Unfortunately, few preventive strategies that have been found to reduce cancer incidence meet these stringent requirements.

Dietary and behavioral interventions would seem to be particularly safe and effective ways to reduce cancer risk. The most obvious and clearly beneficial of these are smoking cessation programs. However, it has been difficult to show that other dietary and behavioral interventions effectively reduce the risk of cancer; this may be for several reasons. First, altering one’s dietary and behavioral practices is particularly difficult, and may require intensive and prolonged behavioral modification. Second, because the carcinogenic effects of a particular diet or behavior are often lifelong, intervention in adulthood may not be effective. Third, many clinical trials in which dietary or behavioral strategies have been tested have not been found to effectively reduce cancer or precancerous lesions (1-3), although several large dietary intervention cancer prevention clinical trials are currently ongoing. Accordingly, there has been a major effort to find additional methods to prevent cancer.

Recent studies have shown that it is possible to greatly reduce the risk of cancer using preventive therapy with vitamins, natural products, or pharmaceutical agents, or with prophylactic surgery. Examples of these strategies to reduce cancer risk include the use of tamoxifen to reduce breast cancer risk (4), the use of retinoids to reduce second primary head and neck tumors (5), and prophylactic mastectomy or oophorectomy to reduce the risk of breast and ovarian cancer (6, 7). Whereas these preventive interventions have been shown to reduce risk by 50% to 90%, they also have unwanted effects that are not acceptable to most of the general population. However, such interventions still are potentially useful, particularly in individuals at very high risk of cancer; these individuals are often willing to accept rare to even moderate toxicity to reduce their risk.

The recent concerns about the rare toxicity of chemopreventive agents, such as tamoxifen (uterine cancer and thromboembolic disease; ref. 8), Cox-2 inhibitors (potential cardiovascular toxicity; ref. 9), and aspirin (gastrointestinal hemorrhage and possible hemorrhagic strokes; refs. 10, 11), have led to limited use of these chemopreventive agents. It would be a major step backward in the effort to reduce cancer incidence if effective chemopreventive agents were not used because of risks to the general population. Instead, a reasonable alternative approach would be to use effective agents in individuals at very high risk of cancer in whom the benefits outweigh the risks.

One obvious solution to the problem of serious toxicity from chemopreventive agents is to develop safer and effective cancer preventive therapies. Indeed, many cancer prevention researchers are attempting to develop such safe preventive agents. However, it is equally important to apply current knowledge to reduce cancer risk now. Thus, if one could accurately identify individuals at high risk of cancer, it would be reasonable to use currently available cancer preventive agents to reduce their risk.

An Example of the Importance of Risk Stratification: Breast Cancer Prevention

It is now possible to greatly reduce the risk of breast cancer, either through the use of antiestrogen selective estrogen receptor modulators such as tamoxifen or raloxifene (4) or through prophylactic surgery (prophylactic bilateral mastectomies; ref. 7). Such interventions are clearly associated with risk and therefore are not acceptable to many women. However, these risk reduction measures are currently the most effective way to reduce breast cancer risk, and for many high-risk women are the preferred choices. It is clear that in this case the clinical dilemma now is to accurately quantify an individual’s risk of breast cancer; for certain groups of women this is possible. The best example of relatively accurate risk assessment is the identification of women carrying deleterious BRCA1 or BRCA2 mutations. These women can be informed that they have an extremely high risk of developing breast cancer (~39-65% lifetime risk in mutation carriers within the population (12) and up to 80% risk in families with early-onset breast cancer (13)). These women can use this risk assessment...
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The most accurate risk assessment is currently done for people at risk of toxicity. Currently available risk assessment tools are less useful. The available ways to assess risk include predictions based on the presence of histologic premalignant lesions (such as atypical hyperplasia and lobular carcinoma in situ) or epidemiologic-based predictive models such as the Gail model. Both of these methods are useful to predict the risk of breast cancer in a population of women, but they are much less predictive of an individual’s risk. As women consider cancer risk reduction measures that carry a finite risk of serious unwanted effects (such as thromboembolic disease from selective estrogen receptor modulators), they would be better able to make informed decisions if the risk assessment tools could more accurately identify those at highest risk. Ideally, such risk assessment models will take into account an individual’s genetic makeup, their endocrinologic exposure, as well as environmental exposure to carcinogens. Efforts are now ongoing to use estradiol levels, DNA adducts, and gene methylation status to better assess an individual’s risk of sporadic breast cancer.

The assessment of risk is the goal of molecular epidemiologic studies—to better identify cancer-associated alleles or single nucleotide polymorphisms, DNA mutations, epigenetic DNA alterations, and carcinogen-induced alterations (such as DNA adducts). Many such studies are published in this journal. It is anticipated that the results from these studies will lead to improved individualized cancer risk assessment. These risk assessment tools of the future have the potential to better assess the cancer risk of the individual instead of that of a population.

Individuals at the highest risk are often anxious to reduce that risk, and would be excellent candidates for preventive interventions. By using accurate risk assessment information, it may be possible to reduce the incidence of cancer using currently available options, while minimizing the number of people at risk of toxicity.

Risk Assessment Tools for Other Cancers

The most accurate risk assessment is currently done for individuals carrying cancer-susceptibility gene mutations. Thus, it is now possible to predict the risk of several other cancers, including ovarian, colorectal, and thyroid cancer. Genetic testing for mutations in cancer susceptibility genes causing ovarian cancer (BRCA1 or BRCA2 genes), colorectal cancer (APC genes or mismatch repair genes), or thyroid cancer (ret) can be undertaken, and individuals carrying these gene mutations can be counseled about their high risk (in the case of APC gene mutations, up to 100% chance of developing colorectal cancer). Thus, as with familial breast cancer syndromes, the finding of a cancer-causing mutation in these genes may induce individuals to take fairly drastic steps to reduce their risk of cancer (such as undergoing prophylactic colectomy in individuals carrying APC deletions). Although current risk assessment for familial cancers is done using an individual’s personal history and family history of cancer, future research should be focused on finding molecular markers that can be used, in a similar fashion, to identify individual risk of sporadic cancer with a high degree of accuracy. Once this is achieved, healthy individuals at high risk of cancer will be able to make informed decisions when choosing options to reduce their cancer risk. With further advances in molecular epidemiology and cancer prevention research, it will be possible to continue to reduce cancer incidence by intervening in those individuals most at risk.

References

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