

Distinguished expert series

by Peter Bósze

Strategies for the modification of risk factors in gynecological cancers

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Strategies to modify risk for female or gynecological cancers will vary with our knowledge of the epidemiology, etiology, and specific molecular mechanisms for each individual cancer. In general, cancer preventive strategies have been divided into primary and secondary prevention with primary prevention directed toward the causative factors for a disease. Secondary prevention is classically used in cervical cancer cytology screening programs and is essentially an attempt to identify individuals in a population with preclinical phases of the disease where intervention will impact mortality the most. A vast literature has evolved regarding the epidemiology of most of the common cancers in women. While the specific molecular mechanisms are not completely understood at this time knowledge of contributing factors for many of these tumors is well known. The association of cigarette smoking with lung cancer has been well established and the increasing rates of lung cancer, particularly in women, are directly linked to the increasing number of female smokers in the population. Indeed in many western countries lung cancer deaths have overtaken breast cancer as the most common cause of death from malignant disease in women. Excessive sun exposure without adequate skin protection is another lifestyle activity that is related to the high incidence of skin cancer in certain areas.

Epidemiologically, cervical cancer has been studied extensively with the current data indicating a causal role of exposure to human papillomavirus (HPV), particularly at an early age in this disease.

Hereditary breast and ovarian cancer syndromes are well understood and as more information on human genomics becomes available a clear understanding of the underlying molecular mechanisms of these diseases will be possible and hopefully will result in effective strategies for their control.

Unfortunately, in spite of the vast knowledge that is available regarding risk factors for many of these malignancies we have been unable to influence effective lifestyle changes that could substantially reduce the risk of these malignancies in our population.

Increased efforts in education, research, and commitment – both financial and educational – are required by governments and other social organizations.

Key words: Cancer risk; Gynecological oncology; Human Papillomavirus; Smoking and lung cancer risk.

Introduction

The ultimate goal of any effective strategy for cancer control is to prevent individuals from dying from this disease. Strategies by necessity will vary with our knowledge of a particular cancer and the better we understand its epidemiology, etiology and the specific molecular mechanisms for each individual cancer, the better we will be able to effect a productive strategy for cancer control. Appropriate resources must also be available if the strategies are to achieve their goal.

The purpose of this paper was to review some of our knowledge regarding the risk factors for certain gynecological cancers and to see how this knowledge may then be used to achieve a reduction in cancer deaths.

Cancer prevention strategies have generally been divided into primary and secondary prevention. Primary prevention usually employs strategies directed toward the known risk or causative factors of a disease. Secondary prevention usually uses screening programs, either for specific subsets of the population or for all of the population, in order to help identify disease in a preclinical phase where intervention theoretically will beneficially impact mortality the most.

Primary changes

In order for primary prevention to be effective what is needed is a clear understanding of the epidemiology and etiology of a disease so that the identified risk factors can then be modified or ideally eliminated. Primary prevention strategies are founded on research and education. The focus is to try to educate the population regarding risk factors and then to try to modify lifestyle practices. The classic lifestyle modification has to do with smoking cessation and lung cancer. Excessive sun exposure without adequate skin protection is another activity related to the high incidence of skin cancer in areas where hours of sunlight and its intensity are high. Sunlight exposure, similar to that for smoking, is an environmental factor whose effects are usually only apparent many years after chronic prolonged insult.

Lifestyle changes

Few would argue that cigarette smoking or tobacco use in general is the major factor in the causation and mortality from lung cancer. Indeed in many parts of the world lung cancer has rapidly become one of the most common forms of cancer in women and these changes have been largely attributed to increased use of cigarettes [1-3]. There is a substantial body of evidence [2, 3] from both epidemiologic and toxicology studies indicating the carcinogenicity of smoking tobacco. Cigarette smoking has also been shown to increase the risk, not only of lung cancer, but also of cancer of the oral cavity, larynx, esophagus, bladder, pancreas and kidney. It should be remembered, however, that the effect of cigarette smoking and cancer rates only manifest some 20-30 years after exposure first begins. Obviously women are not immune to the adverse health effects of tobacco smoking with all indications that in several countries lung cancer rates in women will continue to increase for the foreseeable future. In some countries, such as Canada, lung cancer deaths [3] have already overtaken breast cancer as the most common cause of mortality from malignant disease. What is even more worrisome is that the real effect will not be observed for another 20 or more years.

The message is clear – the most effective strategy that can be initiated against lung cancer deaths in women must be based on education and promotion centred around primary prevention. Educational efforts directed at the young are needed to overcome the slick advertising message to young women telling them that smoking is fashionable, a sign of maturity and adulthood. Governments and public health authorities should encourage the banning of advertising of tobacco and tobacco products.

Diet and cancer risk

Probably the second major determinant of cancer risk is associated with complex exposure related to diet, nutrition and dietary practices. It is difficult to quantify the exact mechanisms of carcinogenesis caused by human dietary exposure or practices but as the epidemiological studies on diet and cancer become more sophisticated associations will become clearer and the mechanisms better understood. Some estimates have suggested that as many as 35% of human cancers may be associated with dietary practices.

Much of the research regarding dietary factors [4, 5] in cancer has focused on fat intake as well as the dietary intake of vitamins, meats and vegetables. Obviously, promotion of healthy dietary practices should be encouraged but realistically, in many parts of the world, the ability to effect specific dietary changes will be impacted by economic and cultural factors. Primary prevention, although understood in this regard, may be difficult to bring about.

Infective processes and cancer risks

There is increasing recognition that infective agents and processes are one of the three major identifiable groups of cancer causes. Good evidence [6] has been presented to show that infection with certain hepatitis viruses is related to hepatocellular carcinoma as well as striking associations between Epstein-Barr virus (EBV), nasopharyngeal cancer and EBV infection in Hodgkin's disease in certain countries. Most importantly, from a gynecological point of view however, is the overwhelming amount of evidence [7] implicating infection with certain subtypes of human papillomavirus (HPV) as one of the major causative factors in cervix cancer.

Other general risk factors

Occupational exposure to carcinogens, pollution, food additives, medicines and medical procedures such as radiation therapy, and geographical factors certainly account for some, but definitely only a small proportion, of the total cancer burden in women. Identification of such factors will also help in planning useful primary prevention strategies.

Specific cancers in women

I. Cancer of the Breast

Breast cancer is the most frequently occurring malignancy among women worldwide, and in developed countries it is by far the most common. There is no region in the world with a truly low rate of breast cancer.

The etiology of breast cancer, in spite of many detailed studies, has remained elusive. Hereditary breast cancer although important, probably accounts for only 5% of all breast cancers. Much work has been done in identifying gene mutations of the BRCA-1 and BRCA-2 genes in certain ethnic and familial situations.

Another change in the risk of breast cancer has been noted in migrant women [8, 9], particularly in studies from Hawaii, San Francisco and Japan, where women of Japanese ancestry residing in Hawaii or San Francisco have double the rate of breast cancer than that of their Japanese forebearers. These findings strongly suggest environmental factors as playing a role in the causation of breast cancer.

The fact that the rate is higher among blacks as compared to white members of the same community in many locations in the United States also suggests that a large proportion of breast cancer is related to environmental or lifestyle factors and therefore would theoretically be avoidable if we could identify these specific factors.

a) Risk Factors for Breast Cancer and Preventative Strategies

The risk for breast cancer is increased about 50% in nulliparous compared to parous women. The risk increases with advancing age of first birth [10-12], until a first birth occurring after the age of 35 years which carries a higher risk than nulliparity, indicating that a first childbirth after this age is no longer protective against breast cancer. The association with parity is less clear but in general it appears that there may be some independent contribution of high parity to reducing breast cancer risk. Risk also appears elevated with a late menopause and conversely an early menopause, whether natural or artificial, contributes to reducing risk. Early age at menarche as well as breast-feeding may have some associations but studies [13] are not clear and have conflicting results. Several studies [14-16] have also been done to try to quantify the risk of abortion to breast cancer with certain studies showing that an interrupted pregnancy does not impart the long-term protective effect that a full-term pregnancy does against breast cancer development. In terms of possible preventative strategies, this is important given the large number of induced abortions that are done worldwide and the common nature of breast cancer itself. Other identified risks for breast cancer have included dietary factors such as an increased body mass index in postmenopausal women, as well as studies [17-21] trying to link risk to dietary fat intake which have produced conflicting evidence. Not all fat should be considered in a similar manner, as higher consumption of olive oil as seen in studies [19-21] from Spain, Greece and Italy, may be associated with lower risks of breast cancer. A large number of studies [22-26] have been carried out trying to better identify the relationship between hormone use in the form of either oral contraceptives and hormone replacement therapy and the risk of breast cancer. In summary, women who are using combined oral contraceptives or who have used them in the past ten years are generally thought to be at a slightly increased risk of breast cancer, with the relative risk disappearing after cessation of use for ten or more years. In terms of hormone replacement therapy in perimenopausal and postmenopausal women, the overall risk is also slightly elevated.

Primary prevention strategies in trying to identify risk factors for breast cancer can be utilized in an attempt to produce alterations that ultimately will affect mortality. Secondary prevention, through earlier diagnosis, should increase survival and is the basic principle inherent in mammography screening programs. Their use is however limited mainly to developed countries with sufficient economic resources to carry out such programs. In time women with BRCA-1 and BRCA-2 gene abnormalities, either through a familial

history of breast cancer or because of belonging to a specific ethnic group, may benefit from widespread introduction of programs to identify the aberrant gene in young women so that possible intervention strategies can be introduced at an age before one would normally expect to see the cancer develop. Finally, several studies have now shown that women treated with tamoxifen have approximately a 1/3 reduction in breast cancer risk in the contralateral breast.

II. Cervical Cancer

Cervical cancer is the second most common form of malignancy worldwide with approximately 450,000 cases reported annually. It is also the leading cause of death from malignancy in developing countries. Generally the highest recorded rates in the world are in sub-Saharan Africa as well as Central and South America and some regions of Southeast Asia. Cervical cancer has been one of the most studied of human malignancies and a vast literature [27-30] exists on its epidemiology. This literature has consistently demonstrated a clear association between a woman's risk of developing cervical cancer and the number of sexual partners she or her partner have had. This association strongly suggests that a sexually transmitted agent is involved in the etiology of cervical cancer, with viruses being considered among the most likely candidates. Human papillomavirus infection (HPV) has long been suspected of having a possible role in the causation of cervical cancer. Currently over 70 different types of HPV's have been identified to date with 20 or so having been shown to have oncogenic potential. HPV-16 and HPV-18 are the subtypes most commonly associated with advanced cervical intraepithelial neoplasia and invasive cervical cancer.

The knowledge that cervical cancer resembles a sexually transmitted disease which is inversely related to the age at first intercourse and directly to the number of sexual partners and independently related to multiparity, are all factors that could be used in primary prevention strategies for this disease. Education among young people as to the association with sexual practices, i.e. early age at onset and multiple partners and how such practices can effect their relative risk in developing this disease in the future, can and should be introduced.

Most importantly, a long history of secondary prevention [31] through cervical cancer screening programs in populations has clearly demonstrated the benefits of this approach. Simply utilizing a system whereby women would be screened every three years between the ages of 35 and 65 has been estimated to produce a reduction in the incidence of cervical cancer by over 90%.

Vaccine development and testing is currently underway and offers great hope – particularly in developing countries with high rates of disease and without the resources for screening program implementation.

III. Endometrial Cancer

The epidemiology of endometrial cancer is not unlike that of breast cancer in several respects. Incidence rates are generally reported to be higher in developed countries of North America and Europe with the exception of Japan where they are relatively low. Endometrial cancer is predominantly a disease of older post- or perimenopausal women with a known association with hormone use and body mass index. It is strongly related to elevated levels or availability of exogenous or endogenous estrogens [32-34] and correspondingly low levels of progestins. Thus it appears related to anovulation in many women, where estrogen replacement treatment in menopause and obesity are all factors which increase endogenous estrogen levels and are all factors that can be modified in an attempt to reduce relative risks of this disease. Combined estrogen and progestin medication seems to confer a protective effect leading to a reduced relative risk for this disease. Estrogen treatment may also protect against colon cancer [35].

The obvious preventive strategies that would seem to hold the most prominence at this time is optimizing body weight for individuals and avoiding obesity; hormone replacement therapy is needed and progestin supplementation should be part of the regimen.

IV. Ovarian Cancer

Ovarian cancer is an important gynecological cancer, particularly in the western world where it usually ranks sixth among the most frequent forms of cancer in women. The importance of epithelial ovarian cancer in most countries is that it is the leading cause of death from pelvic malignancy in women excluding colon

and rectal cancers. It is also a disease with no early warning signs or symptoms and the vast majority of cases are diagnosed with stage III or IV disease, where the chances of cure are much lower.

The etiology of ovarian cancer is unknown. The risk of ovarian cancer appears to increase with age and is approximately twice as common in nulliparous women as compared to parous women. An increased risk has also been suggested for late age at first birth, early menarche and late menopause with some protection being suggested by higher parity. The concept of "incessant ovulation" was put forth by Fatahalla in the 1970's and has been one of the basic mechanisms invoked to explain these observations. It is thought that the repeated ovulations produce tears in the surface epithelium and the ultimate repair and regeneration process might subject the cells to influences that ultimately lead to incorporation of surface epithelium into subsurface areas of the ovary encystation and ultimately transformation into malignant epithelium. Several studies [36] have indicated that oral contraceptive use is protective against ovarian cancer with the incidence being reduced by approximately 40% in users and to an even greater extent in individuals who have been long-term users of these medications. Thus on a population scale, the use of combined oral contraceptive tablets has probably been the major determinant of the favorable decrease in ovarian cancer rates observed in many western countries.

Discussion

It is evident that a variety of cancers in women are exceptionally well understood so that effective preventive strategies could be used if the will is present. Obviously, in many instances resources fall far short of what is needed to mount any effective campaign in this regard. All of us can and must, however, have a role in direct patient education and information dissemination, for all this takes is time and effort and when done, is most rewarding to the practitioner.

When programs, projects, or pilot studies are done, one should be specific as to the efficacy, efficiency, and cost effectiveness of the study or program being carried out.

Efficacy is the feasibility of achieving the objectives in an ideal environment whereas the effectiveness is the feasibility of achieving the same objective in the real world with an effective cost-benefit analysis. It must be remembered that not all tumor markers or measures are equally cost effective and thus may not be easily applicable or appropriate in clinical practice. For example, cervical smears are not only effective they can be cost effective in contrast to the current available methodology and screening for ovarian cancer with routine pelvic ultrasounds which would, with the exception of certain well-defined conditions, appear not to be cost effective at this time.

Conclusion

Currently cancer of the lung, breast, skin, cervix and endometrium are all common cancers that could be impacted in a significant fashion with the existing knowledge and technology.

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