THE EPIDEMIOLOGY OF MULTIPLE PRIMARY CANCERS

The Editor interviews:
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Editor: In the past, the phenomenon of multiple primary cancers was considered a medical curiosity. Should it still be regarded in this light?

Dr. Schottenfeld: Since Billroth’s first isolated case reports at the end of the last century, multiple primary cancers have been observed with increasing frequency. As anticipated, multicentric cancers in a single organ, paired organs or in contiguous tissues are now known to occur with excessive frequency. However, there is conflicting evidence regarding the prevalence of multiple primary cancers in different organs or tissues. For example, a 1932 study by Warren and Gates of 1,078 autopsies on cancer patients revealed that 40 patients, or 3.7 percent, had either occult or clinically apparent second primary cancers. More recent necropsy studies have shown that between 5.3 and 8.1 percent of cancer patients have second primary cancers, either occult or clinically apparent, in different organs or tissues.

Editor: Have you and Dr. John Berg also found a relatively high incidence of multiple primary cancers in your study of patients treated at the Memorial Sloan-Kettering Cancer Center?

Dr. Schottenfeld: Our review of 41,341 cancer patients treated at this institution from 1949-1962 has also revealed that multiple primary cancers can no longer be considered rare. Of 5,636 autopsies, we observed 176 (or 3.1 percent) occult second primary cancers in different organs or tissues. In women, the age-specific prevalence ratio did not exceed two percent in patients 20-59 years of age, but increased to 3.6 percent at 60-69 years, 4.8 percent at 70-79 years and rose to 7.0 percent at 80 years and older. In men, the prevalence ratio varied from 1.0-2.1 percent.
in patients 20-59 years of age, and then increased to 5.8 percent at 60-69 years, 9.4 percent at 70-79 years and reached as high as 16.5 percent at 80 years and older.
Clinically apparent second primary cancers in different organs or tissues were observed at an average annual incidence rate of 10.9 per 1,000. This figure was comprised of 368 skin cancers (3.0/1,000/ year) and 981 cancers originating in other sites (7.9/1,000/ year).

Editor: Is the incidence of multiple primary cancers actually increasing or is the increase due to improved reporting?

Dr. Schottenfeld: This is, of course, difficult to determine. I would judge that the apparent trend of increasing frequency is due in part to greater awareness, more diligent clinical and pathological follow-up, and increasing average duration or survival for selected cancer sites permitting the expression of new primary cancers.

Editor: When should the clinician suspect that his patient may have a new primary and not a metastatic lesion?

Dr. Schottenfeld: The term, multiple primary cancer, connotes that the second lesion has a new focus of origin. Therefore, the physician must look very carefully at the morphology of the tumor. When the cell types are distinctively different, the diagnosis of a new primary cancer is clear. On the other hand, when the morphology is similar, especially in contiguous or adjacent tissues, the diagnosis is facilitated by demonstrating foci of in situ or noninfiltrating cancer. As an example, a second primary epidermoid carcinoma of the upper digestive tract would be distinguished from a recurrent cancer by the demonstration of clear margins of resection in the index cancer and in situ foci of origin in the new primary.
However, even with sophisticated histologic techniques, the diagnosis of a new primary cancer is often difficult but should be pursued if there is a high index of suspicion.

Editor: Can the physician predict which patients are most likely to develop a second primary cancer?

Dr. Schottenfeld: To some extent, yes. We have formulated a set of predictive profiles that may aid in the recognition of high-risk patients and ultimately ensure the detection and treatment of early cancer.

Editor: Specifically, what types of patients are included in these predictive profiles?

Dr. Schottenfeld: Because of the significant occurrence of multicentric cancers, the physician should pay special attention to patients with:
an index cancer in a single organ, with respect to a new primary in the remaining tissue; for example, large intestine, urinary bladder and skin.
- an index cancer in a bilaterally paired organ, with respect to a new primary in the opposite organ; for example, breast and lung.
- an index cancer in an anatomical system or tract containing subsites of common embryologic origin; for example, the urothelial surface of the lower urinary tract, female lower genital tract (cervix, vagina, vulva) and anus, and upper digestive tract.

Editor: What is the risk of a second primary cancer occurring in a paired organ, for example, the breast?

Dr. Schottenfeld: The cumulative risk of a new primary cancer in the opposite breast is four percent at five years after the diagnosis of the index cancer, six percent at 10 years, nine percent at 15 years and 13 percent at 20 years. In a woman who developed her index cancer before the age of 50 years—which is often associated with a family history of breast cancer—the annual incidence of a second primary in the opposite breast is almost twice that for a woman who developed her first breast cancer at a later age. Lobular carcinoma in situ is an important predictor of bilaterality.

Editor: Does this imply that patients with heritable forms of cancer have a greater tendency to develop multiple primaries?

Dr. Schottenfeld: A heritable cancer syndrome is characterized by early onset and multicentric foci of disease. The patient who presents with cancer at an earlier than expected age, or who has certain specific precursor or benign neoplastic lesions must be examined carefully and periodically for the development of multiple primary cancers. Conversely, a history of multiple primaries signals the need for monitoring family members who may be at risk of single site cancers or multiple primaries.

The precise role of genetic factors in multiple primary cancer syndromes is unclear, although the list of clinical disorders has become extensive. (Table 1.) As suggested in Table 1, genetic susceptibility may be expressed by the nature and degree of response in various tissues exposed to physical, chemical and biological oncogenic agents.

Editor: What is an example of multiple primary cancers occurring in contiguous tissues, and how do they come about?

Dr. Schottenfeld: In 1970, Dr. Berg and I published a study of 9,415 patients with index cancers of the respiratory or upper digestive tract treated at Memorial Hospital from 1949-1962. During 23,802
| Disorder | Mode of Inheritance | Associated Neoplasms | Commentary |
|----------|---------------------|----------------------|------------|
| A. Large intestine | Autosomal dominant | Intestinal polyps and carcinoma of colon. | Occurs at a frequency of 1/8,000 live births. Cancers are diagnosed at mean age of 40 years. Diffuse mucosal abnormality revealed by cellular kinetic studies with tritiated thymidine. |
| Familial adenomatous polyposis | | | |
| Gardner syndrome | Autosomal dominant | Intestinal polyps, osteomas, fibromas, sebaceous cysts, carcinoma of colon. | May also be seen with carcinomas of the ampulla of Vater, pancreas, thyroid and adrenal. |
| B. Immunodeficiency | Autosomal recessive | Lymphoproliferative neoplasms, leukemia, carcinoma of stomach, brain neoplasms. | Recurrent sinopulmonary infections, cutaneous telangiectasia, mental retardation, progressive cerebellar ataxia, ichthyosis, and abnormalities of cell-mediated and humoral immunity. |
| Ataxia telangiectasia | | | |
| C. Chromosomal fragility | Autosomal recessive | Leukemia, intestinal cancer, bone tumors. | Characterized by various anomalies of growth and development and by chromosomal fragility. Persons with either syndrome or who are heterozygous for either gene have shown an increased sensitivity of their skin fibroblasts to in vitro malignant transformation by the oncogenic virus SV40. |
| Bloom syndrome | | | |
| Fanconi anemia | | | |
| D. Multiple systems | Autosomal recessive | Adrenal cortical neoplasia, Wilms' tumor, hepatoma. | Visceroptomy, cystomegaly, macroGLOSSIA. |
| Beckwith-Wiedemann syndrome | | | |
| E. Nervous and endocrine systems | Autosomal dominant | Adenomas of pancreatic islet cells, parathyroid, adrenal cortex, thyroid and pituitary. May include differentiated carcinomas of thyroid, bronchial and intestinal carcinoma, malignant schwannoma and thymoma. | May give rise to Cushin's syndrome, hyperparathyroidism and Zollinger-Ellison syndrome. |
| Multiple endocrine neoplasia I (Wermer) | | | |
| Multiple endocrine neoplasia II (Sipple) | Autosomal dominant | Medullary carcinoma of thyroid, pheochromocytoma, adrenal cortical and parathyroid hyperplasia. | Elevated serum catecholamines, serum and tissue histaminase. May also give rise to carcinoid and diarrheal syndromes, |
| Multiple endocrine neoplasia III | Autosomal dominant | Medullary carcinoma of thyroid, pheochromocytoma, neurofibromas, subcutaneous neuromas of tongue, lips and eyelids. | |
| Retinoblastoma, bilateral | Autosomal dominant | Bone sarcomas. May also develop brain tumors, melanoma, bladder and bronchogenic cancer. | Radiologic sarcomas with peak incidence within 5-6 years post-treatment. Bone sarcomas also appear outside of irradiated portals. |
| F. Skeleton and soft tissue | Autosomal dominant | Basal cell carcinomas, medulloblastoma, ovarian fibroma and carcinoma. | Skeletal anomalies, digitipathy, palmar pits, ectopic calcification. Heightened cutaneous sensitivity to ultraviolet and X-irradiation. |
| Nevoid basal cell carcinoma syndrome | | | |
| Multiple hamartoma syndrome (Cowden) | Autosomal dominant | Benign and malignant tumors of breast and thyroid, melanoma, papillomatosis of lips and mouth, intestinal polyps and ganglioneuromas. Retropertioneal lipoma, bone, liver and ovarian cysts. | |

*Modified after Mulkihill, J.: Cancer, October, 1977 (In press)
patient-years of observation, 518 second primary cancers were noted. Of these, 73 percent occurred in other respiratory or upper digestive sites. Mutually significant excesses in multiple epidermoid carcinomas were shared predominantly by tissues of the extrinsic larynx, oral cavity, pharynx and esophagus. This finding is compatible with patterns of high alcohol consumption combined with pipe, cigar and cigarette smoking in these patients. Only patients with index cancers of the nasal cavity, paranasal sinuses and nasopharynx did not develop excess cancers.

The latter sites are characterized by a different spectrum of carcinogenic agents and intrinsic susceptibility. The nasal cavity and paranasal sinuses are susceptible to such carcinogens as nickel, chromate, isopropyl oil and radionuclides. Workers engaged in the manufacture of wooden furniture and of leather boots and shoes are at substantial risk of nasal cancer. With respect to the etiology of nasopharyngeal carcinoma, the herpes-type DNA virus of Epstein-Barr is intimately associated with the malignant epithelial cell elements.

We have more recently reviewed the results of a prospective study of patients admitted to Memorial Hospital from 1965-1968 with a single primary epidermoid carcinoma of the oral cavity, pharynx or larynx. A second primary carcinoma of the respiratory and upper digestive tracts was observed at an average annual incidence of 18.2/1,000 in men and 15.4/1,000 in women. Here, too, the risk of developing a new primary was significantly enhanced by intense combined exposure to alcohol and tobacco prior to the diagnosis of the index cancer.

A common etiology may also explain, we believe, the more complex issue of multiple primary cancers in different organs or tissues.

**Editor:** What would help the physician predict patients at risk of multiple primary cancers in different organs?

**Dr. Schottenfeld:** Several interesting positive associations have been observed in our study of more than 40,000 cancer patients and by other investigators, as well. For example, the following patterns have been established:

- breast, ovary, endometrium;
- large intestine, breast, female genital tract;
- leukemias, lymphomas and skin.

The study of multiple primary cancers in these different organs is extremely important from the standpoint of clinical management and the pursuit of clues to common etiology.

**Editor:** More specifically, what are the risks of multiple primary cancers occurring in the breast and female genital tract?

**Dr. Schottenfeld:** In a previous study of 9,792 women with breast cancer, Dr.
Berg and I found that ovarian cancer accounted for 10 percent of all new primaries. The incidence of a clinically apparent new primary cancer of the ovary was twice the normal risk, although only one-tenth the risk of incurring a new cancer in the opposite breast. A mutual relationship was apparent in 921 women with index cancers in the ovary. Here the risk of a new primary breast cancer was three to four times the norm.

Similarly, in postmenopausal women there was a positive relationship between primary cancers in the breast and endometrium. In a 1963 study of patients in the Connecticut cancer registry, Bailar observed that women with endometrial cancer had a 1.5 times higher expectation of developing breast cancer. Schoenberg studied a similar population of women with breast cancer and found that the subsequent risk of a new primary carcinoma in the corpus uteri or ovary was approximately doubled.

Interestingly, the incidence of metachronous ovarian or breast cancer was not significantly increased in 2,529 women with epidermoid carcinoma of the uterine cervix, vagina or vulva.

**Editor:** The demonstration of a positive association of multiple primary carcinomas of the breast, ovary and endometrium certainly suggests etiologic factors common to these diseases.

**Dr. Schottenfeld:** This is indeed the case when one reviews the positive correlations of breast, ovarian and endometrial cancer mortality and incidence rates in various populations, as well as the changing patterns of cancer mortality in migrants and their offspring. For example, when compared with women from the United States and Europe, Japanese women have substantially lower age-adjusted mortality and incidence rates for cancers of the breast, ovary and endometrium. In contrast, the rates for uterine cervix cancer are higher in Japanese than United States white women.

Migrant studies provide a unique opportunity to evaluate the etiologic role of changing environmental factors. In a study reported by Haenszel and Kurihara in 1968, it was noted that age-specific death rates for breast cancer in Japanese migrants and their United States-born offspring were higher than in women in Japan, but still lower than the new host population. Similarly, the mortality from ovarian cancer and uterine corpus cancer increased among migrants and their offspring, although the risks were less than in United States women.

More recent data from the Third National Cancer Survey has shown that the incidence of breast cancer during 1969-1971 in first generation Japanese immigrants 35-64 years of age living in the San Francisco Bay area had increased to almost three times that of women in Japan, and in immigrants 65-74 years it was more than seven-times the rate in native Japanese women, implying an etiologic role for environmental factors.
Editor:  Do these studies suggest an interplay between exogenous and endogenous factors?

Dr. Schottenfeld:  Epidemiologic and experimental studies emphasize the importance of endogenous genetic, endocrine and immunologic factors in the natural history of cancers of the breast, ovary and uterine corpus. However, the studies in migrant populations suggest that these endogenous factors are modified by environmental factors. Although we are still uncertain about the precise nature of these exogenous factors, a major hypothesis concerns dietary fats and estrogen metabolism.

The familial or genetic and endocrine determinants of ovarian cancer vary in relation to histopathologic classification. It was the lack of agreement in the past on standardized international reporting of histological types of ovarian cancer which obscured the epidemiologic features of the epithelial, stromal and germ cell tumors. In general the papillary and serous cystadenocarcinomas of the ovary predominated in the families susceptible both to breast and ovarian cancer and in at least the study by Joly and his associates, there were similar past reproductive experiences of non-parity, delayed age at first pregnancy and increased frequency of spontaneous miscarriages.

Editor:  The association of lymphomas, leukemias and skin cancers seems particularly interesting. Can you offer an explanation?

Dr. Schottenfeld:  The risk of multiple primary cancers in these sites is quite high. In our study, the risk of skin cancer—basal cell, squamous cell and melanoma—was increased five-fold in patients with Hodgkin’s disease, six-fold in lymphosarcoma, 10-fold in lymphatic leukemia and 21-fold in myeloid leukemia. The risks were higher in men after age 40 and were highest in both sexes in the fifth decade.

When primary skin cancer develops after the diagnosis and treatment of leukemia or lymphosarcoma, the carcinogenic effects of irradiation or chemotherapy must be considered. The observation that patients receiving immunosuppressive therapy following renal transplantation are at increased risk of developing lymphoreticular and skin cancers suggests an alternative pathogenic model.

Editor:  Then multiple primary cancers may be iatrogenically produced?

Dr. Schottenfeld:  Radiation therapy may lead to the development of leukemias, sarcomas and carcinomas generally after a latency period of at least five years. In a retrospective cohort study, reviewed in 1973 by Li, of 410 survivors of childhood cancer, the cumulative proportion of children developing second primary
cancers was 12 percent within 5-20 years after initial treatment. Whereas 0.7 cancers were expected based upon cancer rates for the general population, 15 were observed. The majority of second primary cancers were in the field of prior radiotherapy.

Arseneau’s report in 1972 that intensive combination chemotherapy actually potentiates the carcinogenic effect of extended field or intensive radiation in patients with Hodgkin’s disease must still be substantiated. Young reported recently that patients with ovarian cancer receiving chemotherapy, in particular with the alkylating agents, demonstrated subsequently a statistically significant, increased risk of acute leukemia. This may also prove to be an issue in the long-term evaluation of adjuvant chemotherapy in patients with primary operable breast cancer and axillary micrometastases. In addition, a 1976 study by Hoover concluded that postmenopausal women receiving estrogen therapy, particularly diethylstilbestrol, for metastatic breast cancer had a significantly enhanced risk of another primary cancer in the uterine corpus. Hopefully, such consequences of therapy will be minimal and acceptable in relation to established benefits of adjuvant and combination chemotherapy.

Editor: To summarize, what aspects should the physician be aware of in facing the phenomenon of multiple primary cancers?

Dr. Schottenfeld: Since multiple primary cancers can no longer be considered rare, the physician should be alert to the possibility of their occurrence. He should also recognize that there is a clear predisposition for a new primary cancer to arise in a single organ, bilaterally paired organs and in contiguous tissues sharing a common susceptibility to various causal factors. In addition, there are established patterns in which multiple primary cancers occur with excessive frequency in different organs or tissues.

The patient manifesting multiple primary cancers may represent a rather unique experiment of nature that may challenge new avenues of investigation into the complex etiology of cancer. The task of predicting those at risk is yet another important dimension in the demanding process of caring for the patient with cancer.

Editor: Thank you, Dr. Schottenfeld.