Landmark Studies
“Today, SEER stands as the model and standard of excellence for cancer registries, both on a national and international scale. Despite the enormous challenges involved in monitoring cancer in the large, mobile, and diverse U.S. population, SEER has succeeded in building an extraordinary resource that has in so many ways galvanized epidemiologic research into the causes and control of cancer.

Visionary in concept, SEER has earned its name with an unprecedented ability to identify emerging trends, geographic variation, ethnic disparities, and other patterns that have provided new directions for epidemiologic research in cancer etiology and control.”

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Surveillance

Surveillance of cancer patterns is the foundation of the SEER network. It has been the primary means of measuring the national burden of cancer through incidence, morbidity, mortality, and survival statistics, as well as evaluation of the impact of cancer-related risk factors. Surveillance includes descriptive studies, geospatial and GIS clusters/outbreaks data, sentinel/signal/early warnings, health disparities, models and methods, and policy data.
Adenocarcinoma of the Esophagus and Gastric Cardia

Studies in the 1980s of esophageal and gastric cancers used data from SEER registries to describe histologic and epidemiological characteristics. These studies described different patterns by age, sex, and race (black/white) and helped to define a set of squamous cell carcinomas and adenocarcinomas that were increasing in the population. Concomitant with similar observations in European countries, an analysis of 1973-1987 cancer incidence data from nine SEER registries showed steadily rising rates of adenocarcinomas of the esophagus and gastric cardia. The rate of increase surpassed that of any other cancer for the time period, including non-Hodgkin’s lymphoma and lung cancer. To learn more about these cancers, a multicenter case-control study was conducted using cancer registry data on recently diagnosed cases in Connecticut, New Jersey, and western Washington state. This study revealed that smoking is a major risk factor for these adenocarcinomas, accounting for approximately 40 percent of cases. Later studies looked into the possible effects of medications on these cancers, using interviews with patients and controls from the same registry areas as the previous study. Following on the finding that regular users of nonsteroidal anti-inflammatory drugs (NSAIDS) are at reduced risk of colon cancer, investigators found that regular users of either aspirin or other NSAIDs are also at reduced risk of adenocarcinoma of the esophagus and gastric cardia. A second study examined a number of common medications that are known to promote gastroesophageal reflux by relaxing the lower esophageal sphincter (LES). The investigators found that people who took asthma drugs containing theophylline or beta-agonists were at higher risk for esophageal adenocarcinoma, and the risk increased with duration of use. However, the study also provided the reassuring finding that use of other LES-relaxing drugs, specifically calcium channel blockers, is not likely to be related to increased risk for these cancers. Worldwide, research continues to investigate this interesting group of cancers.

Selected References


Surveillance, Epidemiology, and End Results Program

Landmark Studies
AIDS-Related Cancers

One of the most notable features of the AIDS epidemic has been the emergence of Kaposi’s sarcoma (KS) as a common malignancy among HIV-infected individuals. In the early 1980s, the number of people diagnosed with KS rose dramatically in some areas. A report using data from the SEER registries confirmed the marked excess of KS in San Francisco by 1981, although the overall SEER rate for nine registries showed only a slight increase. By mid-decade, public health officials believed they saw a hopeful note in the leveling off of reported cases, particularly in San Francisco, which had a high infection rate. However, studies conducted by the cancer registries of the Northern California Cancer Center and the California Tumor Registry proved this to be incorrect. The former used SEER data to demonstrate that both KS and non-Hodgkin’s lymphoma incidence were continuing to increase. The second study linked data from the California Tumor Registry with the San Francisco AIDS Registry to match the incidence of KS for the years 1980-1986. Several hundred records did not match, with cases found in each registry that were not found in the other. When the unmatched and the matched records were properly combined, an increase in KS through 1986 could be seen for the San Francisco area. This work pointed to the need for further investigation into the true incidence of these tumors.

Selected References


Endometrial Cancer and Estrogen

A study based solely on data from eight population-based cancer registries indicated a link between endometrial cancer and menopausal estrogen consumption in an analysis 30 years ago. This particular study opened a large field of case-control epidemiological studies based on data-rich surveillance systems.

The study synthesized various pieces of evidence to reveal that, in all eight geographic areas surveyed, incidence rates of endometrial cancer had risen steadily from 1969 to 1973, in some areas as much as 10 percent per year. The increase was examined as a function of age, in general appearing most frequently in middle-aged and older women.

The increased use of estrogens, especially estrogens prescribed for symptoms of menopause and osteoporosis, was associated with endometrial cancer. Evidence of the link included SEER registry data that showed an unmistakable relationship between estrogen consumption and endometrial cancer and animal studies that indicated that estrogen is a stimulator of hyperplasia in endometrial cells.

The epidemiologic methods used in this investigation were novel at the time. Efficient use of available data made it possible to view exposure to exogenous hormones as potentially risky more rapidly than with a cohort study. More recently, the Women’s Health Initiative followed a large cohort of women until 2002, with a mean followup of 5.2 years. The findings of this large trial concluded that the combination of estrogen and progestin did not significantly raise the risk of endometrial cancer, but did raise the risk of breast cancer. As hormone therapy changes over time, population-based cancer surveillance systems will need to be vigilant in monitoring these cancers.

Selected References


Health Disparities in Underserved Populations

A study in the early 1980s using data from the New Mexico Tumor Registry examined the link between ethnicity and lung cancer in Hispanic and white citizens of New Mexico and found that variations in lung cancer incidence corresponded to differences in smoking patterns between the two populations. Hispanic culture does not promote smoking, and the lower occurrence of lung cancer in Hispanics corresponded to the lower number of Hispanic smokers. This study encouraged the investigation of environmental carcinogens, and supported the connection between smoking and lung malignancies.

A series of studies in the 1980s concluded that poverty, itinerancy, and the resultant restricted access to care can cause high cancer mortality rates in proportion to relatively low incidence rates. Data on the incidence of cancers of the breast, reproductive and gastrointestinal systems, and cancers related to tobacco use from the Louisiana Tumor Registry were compared to SEER data from other geographical areas. Although incidence rates in Louisiana were lower than elsewhere in the country, mortality rates were higher because the cancers were diagnosed at more advanced stages with less favorable outcomes. Another study that examined the incidence of dysplasia and carcinoma of the uterine cervix, which was higher in Appalachian Kentucky than in the overall SEER database, supported a similar conclusion. Likewise, in a study focused on migrant farm workers in California, many of whom were recent Mexican immigrants, lack of access to care, including screening programs, was thought to be the cause of the elevated rate of cervical cancer. Higher incidences of brain cancer and leukemia were attributed to occupational exposures, particularly to pesticides. These studies point to the need for better cancer prevention and early detection programs, especially for cancers that can be treated effectively if diagnosed in time.

Selected References


Cancer Incidence in U.S. Immigrant Populations

Between 1975 and 2003, a number of studies were published that compared patterns of cancer incidence in U.S. Caucasians, immigrant groups, and matched controls. The studies used data from SEER, regional cancer registries in the United States, and cancer registries in other countries. Their conclusions have been remarkably uniform.

The studies found that cancer incidence patterns among first-generation immigrants were nearly identical to those of their native country, but through subsequent generations, these patterns evolved to resemble those found in the United States. This was true especially for cancers related to hormones, such as breast, prostate, and ovarian cancer and neoplasms of the uterine corpus and cancers attributable to westernized diets, such as colorectal malignancies. The longer people lived in the United States, the lower their rates of cancers that could be attributed to Asian diets, such as stomach cancer associated with the highly salted and nitrite-containing foods common in Asia; cancers caused by infections, such as liver cancer caused by hepatitis B and C; stomach cancer caused by Helicobacter pylori; cervical cancer caused by human papillomavirus; and cancers caused by specific environmental problems, such as nasopharyngeal cancer associated with exposure to smoke from stoves used for cooking in the home and salivary cancer associated with cold, dark environments that produce vitamin A deficiencies.

The populations studied included first- and second-generation Japanese immigrants living in Hawaii; Asian-American women; Vietnamese-Americans; Hmong refugees from Vietnam, Laos, and Thailand who settled in California; Korean-Americans; Pacific Islanders; and Alaska Natives. All of these studies helped scientists to identify environmental factors that encourage cancer to develop and paved the way for the field of cancer prevention.

Selected References


Prostate-Specific Antigen (PSA) Testing

The prostate-specific antigen (PSA) test was approved by the U.S. Food and Drug Administration in 1986 for monitoring disease status in men with prostate cancer and in 1992 for diagnosis. Once approved, the test also was performed on men with urological symptoms as well as on those who were asymptomatic in an effort to diagnose prostate cancer early and affect the mortality rate. Use of the test since 1986 was correlated with a dramatic rise in prostate cancer incidence in the early 1990s, followed by a subsequent decline. Rates have recently resumed the pre-PSA trend. The incidence of distant stage disease, which had been relatively flat, started to decline dramatically in the early 1990s. Prostate cancer mortality also began to decline in the early 1990s, and the decline has continued. Randomized controlled trials have not yet confirmed the efficacy of PSA testing, which raised the question of the role played by the PSA test in the recent mortality decline. It was important that NCI answer this question to provide the public and cancer researchers with an informed judgment about the impact of the PSA test on vital statistics in light of a pattern in the rates that suggested a benefit from use of the test.

Modeling efforts to understand these patterns used data from autopsy studies, SEER, the SEER-Medicare linked database, mortality data from the Centers for Disease Control and Prevention, and population estimates from the U.S. Census Bureau. Studies of the incidence patterns estimated that approximately 29 percent of white males and 44 percent of black males were overdiagnosed, an important problem associated with the high prevalence of PSA-detected disease in older men that would not have progressed to symptomatic disease prior to death from other causes. Other findings concluded that if PSA screening was as effective as hypothesized in the major U.S. randomized screening trial, then it could be responsible for a large portion, but not all, of the observed mortality decline. The delay in seeing the full potential mortality benefit of PSA screening is associated with the speed of dissemination of PSA screening, the lead time inherent in screen-detected cases, the size of the survival benefit, and the range of survival times that would have occurred in the absence of screening.

Selected References


Surveillance

Lifetime Risk of Breast Cancer

The lifetime risk of developing breast cancer is a commonly cited statistic. Many estimates of this figure have been derived using cancer rates for the total population. However, when explaining risk, we usually are referring to the cancer-free population rather than the total population. In 1993, collaborators from NCI, SEER registries, and the American Cancer Society published a revised method for calculating estimates of lifetime risk based on SEER data from 1975-1988. The data were adjusted so that the incidence reflected only first primary breast cancer; mortality included causes other than breast cancer. The population denominator for incidence was adjusted to reflect only women with no previous diagnosis of breast cancer. The calculations showed an overall lifetime risk for developing invasive breast cancer of one in eight women, derived from the 1987-88 data. In comparison with the figure for 1975-77 (1 in 10.6), the lifetime risk of developing breast cancer rose. Lifetime risk of dying of breast cancer remained generally flat. A large portion of the rise in risk of developing breast cancer may be attributed to early detection of prevalent cases due to increased use of mammography screening and lower mortality due to causes other than breast cancer (for example, coronary heart disease). In other words, more women are being screened for breast cancer, and they are dying less often of other causes. This study enabled researchers to develop an enhanced expression of the assessment of breast cancer risk as it relates to age and provided physicians with a more meaningful context in which to communicate this risk to their patients.

The interest in communicating risk led scientists at the NCI and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to develop the Breast Cancer Risk Assessment Tool. This tool allows health professionals to project a woman’s individualized estimate of risk for invasive breast cancer over a 5-year period and during her lifetime. The tool uses data from the Breast Cancer Detection and Demonstration Project, a mammography screening project involving over 280,000 women that was conducted in the 1970s. The Breast Cancer Risk Assessment Tool may be used by clinicians for clinical counseling purposes, such as recommending mammography at a younger age, or having more frequent clinical breast examinations, or providing reassurance to many women who had previously overestimated their risk of breast cancer.

Selected References


More information about breast cancer risk assessment can be found at http://bcra.nci.nih.gov/brc/
Surveillance

Geographic Surveillance

Maps have long been used in surveillance of disease and in epidemiologic investigations. New technology using global positioning systems (GPS) coupled with geographic information systems (GIS) has revolutionized the field of geographic surveillance. Investigators associated with the SEER registries have started to use this technology to enhance cancer surveillance, fill gaps in surveillance coverage, find new cases of cancer, and reduce cancer mortality.

In 2003, a New Jersey state report summarized the analytic results confirming a statistically significant increase in childhood cancers for the period 1979 to 1995 in Dover Township. This increase was due primarily to excess leukemia, brain, and central nervous system cancers in females less than 5 years old. A case-control analysis revealed increased association for leukemia in young girls and high exposure to well water in proximity to a Superfund industrial site. An elevated association between leukemia and postnatal exposure to private well groundwater for both males and females was observed. Prenatal exposure to ambient air pollution was associated with leukemia among girls aged 0 to 4 years.

A second investigation examined access to mammography clinics among recently diagnosed breast cancer cases in New Jersey using spatial statistics in conjunction with a GIS analysis. Geographic analysis based on place of residence identified two areas in northeastern New Jersey with significantly high proportions of women with distant stage breast cancer. The women who had a later stage of breast cancer at diagnosis in these two areas differed from other late stage cases in the rest of the state; they were older (65+), more likely to be a minority, were less educated, less likely to be employed, and were more likely to be isolated linguistically (primary spoken language not English). Some of these women lived only a short distance from a mammography facility. The New Jersey registry/department of health is using these results to more effectively target populations for cancer screening with the goal of reducing mortality from breast cancer.

Selected References


“SEER is a mainstay of the National Cancer Program – it provides baseline cancer rates and focuses our research on the most important problems. It is the backbone for studies of environmental influences on the development of cancer, for examination of cancer survival among the many segments of our population, and for measuring our progress against cancer for the Nation as a whole. Rational leadership of NCI would not be possible without SEER.”

Peter Greenwald, M.D., Dr.P.H.

Director, Division of Cancer Prevention, NCI
Epidemiology

The area of cancer epidemiology has benefited immensely from the SEER network, a key resource not only for descriptive and correlational studies of cancer in the United States, but also for population-based case-control and cohort studies. SEER is often where changes in cancer incidence and death rates are first detected, stimulating additional epidemiologic investigation to reveal the cause. In the last 30 years, SEER has significantly helped to increase the depth and breadth of epidemiologic studies to include environmental exposures, geographic determinants, diet, reproductive factors, physical activity, genetic factors, and biological determinants of disease.
Agricultural Health Study

The Agricultural Health Study (AHS) began in 1993 as a collaborative effort to elucidate the health risks posed by exposure to agricultural pesticides and other potential hazards of farm work. Agricultural workers and their families in Iowa and North Carolina were invited to participate in this cohort study. Current enrollment includes 89,658 individuals. For individuals who developed cancer during the study, case information was collected in Iowa from the Iowa Cancer Registry (ICR), a site that has been affiliated with the SEER program since 1973. Although the North Carolina Central Cancer Registry is not affiliated with SEER, this registry represents a racially and ethnically diverse agricultural population within the United States.

In May 2003, the first publication of cancer findings from the AHS appeared. The paper focused on prostate cancer and revealed a slightly increased risk for prostate cancer associated with the use of the fumigant methyl bromide. Risk for prostate cancer increased with higher levels of exposure to methyl bromide. Intensive analysis of personal exposure data to this compound and others will supply scientists with a further understanding of the etiology of prostate cancer. Future publications on other cancer sites in association with exposure data from the AHS will include breast, lung, colon, non-Hodgkin’s lymphoma, multiple myeloma, and leukemia.

The results from a nested case-control study on high pesticide exposure events (HPEE) indicate that occurrences of unusually high personal exposure to fertilizers and pesticides are occurring at an increased frequency with unknown health impacts. The results from a reliability study pointed to the advantages of using data gathered for epidemiologic purposes in contrast to agriculturally relevant data from other sources not intended to evaluate human health. The results of a study on self-administered exposure questionnaires and sampling provided additional insight into collecting this kind of personal exposure data efficiently and with reasonable results that can be widely applied in a research setting.

Selected References


For more information, please see http://www.aghealth.org/
Epidemiology

National Bladder Cancer Study

In 1978, the National Bladder Cancer Study (NBCS) inaugurated use of the entire SEER network to mount a large and rapid study to address a critical issue in cancer epidemiology. Prompted by the U.S. Food and Drug Administration’s need to determine whether consumption of saccharin increased the risk of developing bladder cancer, investigators at the NCI and in ten SEER centers conducted the largest and most detailed investigation of bladder cancer to date. Interviews from nearly 3,000 cases and 6,000 controls provided an unprecedented opportunity to examine occupational, environmental, medical, and lifestyle influences on risk and resulted in dozens of reports in peer-reviewed journals. The study clearly demonstrated the power of SEER for epidemiology and led to wide use of the resource for population-based cancer research.

The study uncovered excess bladder cancer risk in truck drivers, workers exposed to motor exhaust, and workers within the chemical, rubber, and plastics industries. In addition to the known link to cigarette smoking, a link to the use of pipes or cigars emerged from the study, along with a detailed understanding of the beneficial effect of stopping smoking. Exposure to chlorination byproducts in drinking water supplies, a common environmental exposure, was associated with increased risk. People who had suffered three or more urinary tract infections also showed increased risk, as did those with bladder cancer in the family.

Several widespread exposures that had been suspected of increasing bladder cancer risk, including the use of saccharin and other artificial sweeteners, the consumption of coffee and tea, and the use of hair coloring products, were found to be unrelated to risk in this large, detailed study. Because the study included large numbers of women and African-Americans, it afforded unique opportunities to compare risk patterns in those groups to the white male majority. In addition, because the SEER network reflects the population at large, the male excess risk and the white excess risk could be separated according to the factors responsible.

Selected References


Environmental Tobacco Smoke and Lung Cancer

Following several reports of the Surgeon General on the consequences of involuntary smoking, the U.S. Environmental Protection Agency (EPA) released a report in 1993 in which environmental tobacco smoke (ETS) was labeled a human carcinogen. The report was based on 30 epidemiologic studies from around the world, including a large multicenter case-control study involving SEER registries. The study used a questionnaire specifically designed to evaluate the role of ETS exposure in the development of lung cancer among lifetime nonsmokers. The study revealed that any exposure from a spouse who smoked was associated with at least a 30 percent excess risk. Findings from the first 3 years of the study contributed the greatest individual study weight to the relative risk estimates for lung cancer in the EPA report. After completion of 2 additional years of subject accrual in 1994, the investigators confirmed excess risk among women exposed to ETS in the household, in the workplace, and in social settings. Another interesting finding was the predominance of a particular histology, adenocarcinoma, supporting the theory that sidestream smoke differs in character from mainstream smoke and that the type of inhalation, nasal rather than oral, can affect the deposition of vapor and particles in the lung.

At the same time, researchers were examining other health outcomes of exposure, and studies were done in the workplace to measure nicotine concentrations in office air where smoking was permitted. The cumulative results of these investigations motivated the American Medical Association to review the evidence and join with other organizations in a call for the health community and government regulatory agencies to deal with this threat to public health. Since that time, smoking policies have been developed for workplaces, transportation, and other public sites to prevent the involuntary inhalation of tobacco smoke.

Selected References


Epidemiology

Cancer and Steroid Hormone Study

The Cancer and Steroid Hormone (CASH) Study was a population-based, case-control study conducted by eight SEER registries during the 1980s to investigate the relationship between oral contraceptive (OC) use and breast, endometrial, and ovarian cancers among U.S. women. The CASH Study found that current or former OC use did not appear to be associated with a significantly increased risk of breast cancer. Such use did appear to decrease the risk of developing ovarian cancer, and the risk of ovarian cancer also appeared to decrease with longer duration of OC use and remained low long after use was stopped. Exclusive use of combination OCs (in which the daily dose contains estrogen plus progestin) appeared to have a protective effect against the development of endometrial cancer. Users of sequential OCs (in which each monthly cycle consists of several days of estrogen followed by fewer days of estrogen-plus-progestin) and of all other OCs (unknown, progestin only, or two or more other OC types) were at greater risk of developing endometrial cancer than were women who had never used OCs.

Among naturally menopausal women, the risk of breast cancer appeared to increase with increasing body mass index. Severely overweight women had nearly a threefold higher risk of breast cancer compared with the leanest women. This trend appeared stronger with increasing years since menopause. A positive association between body mass and breast cancer risk also was observed for premenopausal women, although risk estimates were lower. Substantial weight gain from adolescence to adulthood was a more important risk factor than was lifelong obesity.

A more recent study, the Women’s Contraceptive and Reproductive Experiences (Women’s CARE) study, corroborated the earlier findings that OC use does not appear to increase the risk of breast cancer in women. This study included women, 35 to 64 years old, who had invasive breast cancer initially diagnosed between 1994 and 1998. The SEER registries in Atlanta, Detroit, Los Angeles, and Seattle provided support for this study.

Selected References

Centers for Disease Control Cancer and Steroid Hormone Study:


Epidemiology

Women’s Interview Study of Health

The Women’s Interview Study of Health (WISH), a population-based case-control study conducted during the early 1990s, focused on identifying risk factors for early onset breast cancers. The study was conducted by NCI and included newly diagnosed breast cancer patients from the SEER areas of Atlanta and Seattle and from ten counties of central New Jersey. Given the relatively young age of study participants, a major focus of the study was on factors early in life that might be predictive of the subsequent occurrence of breast cancer. These included use of oral contraceptives (OCs), developmental history, physical activity, diet (including alcohol consumption), and cigarette smoking. The study also addressed the role of pre- and postnatal factors that have been postulated to have an effect on subsequent breast cancer risk.

Results from the study showed that recent use of OCs, especially long-term use, increased the risk of very early breast cancers, namely those that develop prior to the age of 35. Notably, recent OC users who had been exposed for 10 or more years were at approximately a twofold increased risk compared with nonusers. An analysis of the dose of estrogens and progestins used provided support for the notion that the elevated risks may have been due to the higher formulations that were used in early years. Alcohol consumption also was identified as a major predictor of risk, although early life exposures were no more predictive of risk than were later exposures. Although body size was found to be predictive of risk, components of diet and physical activity could not be linked definitely with this relationship.

This study provided support for the notion that very early life exposures have an effect on subsequent breast cancer risk. Notably, twins—particularly women with a twin brother—were at an increased risk compared to singletons, a finding that is consistent with the observation of high estrogen levels in dizygotic twin pregnancies. In addition, a reduced breast cancer risk was observed among women who had been breastfed as infants. This finding requires further exploration, including an underlying biologic explanation.

Selected References


Epidemiology

Black/White Cancer Survival Study

In the early 1980s, a group of investigators proposed to examine the possible social, behavioral, and biological determinants of disparities in cancer survival between black and white cancer patients. The Black/White Cancer Survival Study focused on four common cancers—breast, colon, bladder, and endometrial—which were among those with the greatest racial disparities in survival reported by SEER and the earlier End Results Group. SEER cancer registries in Atlanta, San Francisco, and Louisiana participated in the study, gathering additional information on patients diagnosed from 1985-1987. The original hypotheses guiding the study were: Do lower levels of cancer screening and preventive behaviors among blacks lead to later stages of cancer at diagnosis? Are histological characteristics of tumors in blacks different from those in whites? Do black patients receive less aggressive therapy or have lower treatment compliance compared with whites? How do variations in social support and coping strategies among blacks affect cancer outcomes?

During the following two decades, more than 50 collaborators published more than 20 analyses that examined these questions. Among the results, researchers found that, although stage at diagnosis and access to health care played a part in lower survival rates for blacks, they could not account for all of the disparities found. Even after survival was adjusted for sociodemographic and lifestyle factors and for treatment patterns, differences remained. For breast and endometrial cancers, black women usually were found to have tumors that grew faster, were less responsive to therapy, and carried more poor prognostic features at baseline than did their white counterparts. For colon cancer, more aggressive tumor characteristics did not explain racial differentials in survival, which suggested that other environmental exposure factors and the need for improved biomarker measures of tumor biology and host susceptibility. Blacks were less likely than whites to develop bladder cancer. Once diagnosed, however, blacks experienced poorer survival, primarily due to a greater extent of disease at diagnosis and higher tumor grade. Socioeconomic factors were associated with racial differences in bladder cancer, suggesting that risk and/or prognosis may be mediated by occupation and lifestyle factors, a topic for further study. Followup and analysis of long-term survival is possible for this SEER study cohort.

Selected References


Nonsteroidal Anti-Inflammatory Drugs and Cancer Prevention

Numerous studies have provided evidence that nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, may hold promise in helping to prevent cancer. Experimental and epidemiologic (nonrandomized) studies, along with randomized clinical trials, have shown that NSAIDs may have a prophylactic effect against certain cancers. These results have been confirmed in certain colorectal cancers and suggested for other cancer sites.

The idea that NSAIDs might inhibit the occurrence or growth of colorectal cancers was developed in the 1970s and led to a series of animal experiments. Later, randomized clinical trials established that two NSAIDs (sulindac and celecoxib) suppress adenomatous polyps and cause existing polyps to regress in patients with familial adenomatous polyposis (FAP, a rare hereditary condition). Evidence from epidemiologic studies has shown that people who report regular NSAID use have a lower incidence of adenomatous polyps and lower colorectal cancer death rates, indicating a possible protective effect from NSAIDs for the general population. Two recent randomized clinical trials confirm that aspirin suppresses the recurrence of adenomatous polyps in persons with a previous polyp. More limited epidemiologic data show that NSAID use may be associated with lower incidence of or death from cancers at other sites, including the esophagus, stomach, breast, lung, prostate, urinary bladder, and ovary.

Studies are ongoing to determine how NSAIDs may protect against various cancers, possible effects of the long-term use of these drugs, optimum dosages, and contraindications. Benefits and risks of NSAID treatment across a broad range of treatment regimens, outcomes, and patient populations also are being studied.

Selected References


Epidemiology

Genetic Susceptibility Studies

The recent identification of genes associated with susceptibility to breast, colon, or other cancers highlights the importance of identifying families with hereditary patterns of cancer. Familial cancer registries are an important tool enabling researchers to identify genetic and environmental changes that modify cancer risk and apply the resulting knowledge to cancer prevention and control. The Breast and Colon Cancer Family Registries were established in 1997 as an international consortium to provide a research infrastructure for genetic and epidemiologic studies of these and related cancers, including characterization of already known genes and identification of new genes. The twelve participating institutions collect and maintain detailed information about cancer risk factors and molecular and clinical information from nearly 15,000 families and more than 6,000 population controls. A repository of blood and tissue samples from family members also has been established for research purposes. The SEER registry infrastructure has been critical both to the recruitment of these families and to the retrieval of related cancer data. Various interdisciplinary studies is underway, the results of which ultimately will be applied to the design of targeted preventive and therapeutic interventions.

The Women’s Environment, Cancer, and Radiation Epidemiology (WECARE) Study is a multicenter, population-based study of women with breast cancer that is investigating gene-environment interactions that may influence susceptibility to this disease. The study has established a repository of epidemiologic risk factor information and biologic specimens from 2,100 women drawn from five population-based tumor registries in the United States and Europe. Beyond the major research questions that are the focus of these registries, issues such as informed consent and standardization of methods critical to conducting studies that use families across multiple centers also are being addressed. In addition, researchers are being afforded the opportunity to examine questions that surround the validity of family history data and optimal designs for estimating the frequency of mutations of disease-susceptibility genes.

Selected References


Gene for Melanoma

Identifying major susceptibility genes for cancer is the first step in better understanding the epidemiology and genetics of cancers with hereditary patterns. Registry data can play a critical role in these studies. An example is the identification of CDKN2A, the first major melanoma susceptibility gene to be discovered.

In 1994, the CDKN2A gene was localized to chromosome 9p21, a region that had been implicated previously in familial melanoma in linkage, cytogenetic, and loss of heterozygosity studies. Subsequent mutational analysis in familial melanoma-prone families led to the determination that CDKN2A was a melanoma susceptibility gene. Data used in several of these studies came from the Utah Cancer Registry, a population-based cancer registry that has been in existence since 1966. It is one of the original members of NCI's SEER Program and has continuously participated since 1973.

In addition to contributing to the identification of major susceptibility genes, registry data also can be critical to examining penetrance, modifying genetic and environmental factors, recognizing gene-environment interactions, and determining frequencies of mutations in disease susceptibility genes.

Selected References


Diet and Cancer

Hawaii has been the setting for numerous successful diet-related studies, using the Hawaii Tumor Registry (HTR) as the primary resource for identifying individuals with cancer. Previously, studies of dietary effect on cancer risk were few and inconsistent, usually based on estimates derived from per capita food consumption data. SEER data, with its breadth and depth of content and chronology, combined with the careful design and implementation of the study methods, gave strength to the results of these investigations and laid a foundation for future research in this provocative field.

In-person interviews were conducted by trained interviewers using detailed questionnaires on pertinent habits (e.g., smoking) and food consumption—types of food, frequency of consumption, and portion sizes, over time. Appropriate variables were adjusted for, and standard methods were used to analyze the resulting data.

Based on a selection of thirteen studies, the following increased risk associations were suggested: dietary cholesterol with lung and laryngeal cancers; alcohol consumption with rectal and lung cancers; fat consumption with endometrial, breast, prostate, and stomach (fish fat only) cancers; well-done red meat with colorectal cancer, but only among smokers with a certain genetic susceptibility; low serum pepsinogen I level with stomach cancer; hepatitis B surface antigen with primary hepatocellular carcinoma; and infection with Helicobacter pylori (gram-negative spiral bacteria that are associated with chronic gastritis) with gastric carcinoma. The following decreased risk associations were suggested: fiber, soy products, and other legumes with endometrial cancer; dairy calcium and lactose with ovarian cancer; beta-carotene, overall vegetable consumption, and vitamin A with lung cancer; and carbohydrate intake with breast and corpus-uteri cancers. No associations were found for dietary vitamin C and cancer.

Selected References


Epidemiology

Physical Activity and Cancer

The 2002 International Agency on Research Against Cancer Report, *Weight Control and Physical Activity*, indicated that physical activity is likely to have a substantial preventive effect for cancers of the colon and breast. In addition, research is expanding on the role of physical activity in improving the quality of life among cancer patients and cancer survivors, and on its potential beneficial effect on prognosis and survival. Several studies within the SEER registry program have contributed to this body of evidence. Two population-based studies using participants from the Los Angeles Cancer Surveillance Program revealed that physical activity greatly reduces the risk for colon cancer in men and breast cancer in women. In addition, a collaborative effort across SEER registries in the Los Angeles County area, New Mexico, and Seattle is examining the combined effects of physical activity, weight, and diet on breast cancer prognosis.

Researchers selected 2,950 men diagnosed with colon cancer and categorized them according to occupation, grouped by level of activity involved in the job: sedentary, moderately active, or highly active. The study demonstrated that colorectal cancer risk increased as activity level decreased. This gradient was consistent for all socioeconomic factors, for whites, blacks, immigrant and native Hispanics, and for each subsection of the colon. The effect of physical activity on the colon is consistent with the evidence supporting dietary influence on the causes of cancer and other diseases, and the researchers urged further study of dietary effects on cancer risk.

The breast cancer case-control study conducted by the Los Angeles SEER registry evaluated the effects of physical exercise on breast cancer risk in women aged 20-40 years. In all cases, controlling for numerous variables, the risk of breast cancer significantly declined with increasing amounts of lifetime physical exercise. The investigators proposed that habitual physical activity can alter menstrual function, which reduces the cumulative exposure to the carcinogenic effects of progesterone and estradiol.

The HEAL (Health, Eating, Activity and Lifestyle) Study of Breast Cancer Prognosis is examining the effect of physical activity, weight, and diet on breast cancer prognosis among a multiethnic cohort of women with early stage breast cancer. Initial results from this study have found that physical activity levels were reduced significantly after patients were diagnosed with breast cancer. Greater decreases in physical activity were observed among women who were overweight at the time of diagnosis of breast cancer. These results suggest that declines in physical activity may contribute to weight gain commonly experienced during breast cancer treatment, which has been found to have an adverse effect on prognosis.

Selected References


End Results

End Results in cancer have been evaluated by clinicians, epidemiologists, and health service researchers in various ways, including patterns of care, quality of life, years of survival, and the chance of developing a second malignancy. The trends in cancer survival and mortality, along with incidence, cost/economics, and policy, provide critical benchmarks by which the cancer research enterprise in the United States can measure the progress made against this disease.
Patterns of Care

The SEER Patterns of Care (POC) studies provide important information on cancer treatments as documented in hospital records. The study goals are to evaluate the diffusion of state-of-the-art cancer therapy into community practice, disseminate findings in scientific journals and through professional meetings, and work with professional organizations to develop educational opportunities to increase the use of state-of-the-art cancer therapy and quality of care in community practice.

Each year, NCI selects different cancer sites to be included in the POC studies and randomly samples cases from those ascertained by the SEER registries. Cancer sites that have been addressed by POC studies include breast, colorectal, bladder, head and neck, melanoma, non-small cell lung, leukemia, cervical, prostate, pancreatic, testicular, non-Hodgkin’s lymphoma, multiple myeloma, chronic lymphocytic leukemia, vulva, gastric, corpus uteri, sarcoma and ovarian cancers, plus childhood acute lymphocytic leukemia (ALL), acute myelocytic leukemia (AML), Hodgkin’s, osteosarcoma, Ewing’s sarcoma, and brain stem. These studies provide national, population-based information on treatment dissemination into community practice, possible determinants of dissemination, and variations in therapy. This information is vital in developing educational programs designed to improve the quality of cancer care.

The SEER Program provides information that may lead to findings on cancer risk, protective factors, and treatment modalities. The POC studies provide information that may decrease disparities in treatment and survival among different population groups.

Selected References


Prostate Cancer Outcomes Study

The Prostate Cancer Outcomes Study (PCOS) was initiated in 1994 by researchers at the NCI to investigate how prostate cancer and its treatments affect the quality of life of men with the disease. SEER cancer registries in six geographic regions—Connecticut, Utah, New Mexico, and the metropolitan areas of Atlanta, Los Angeles, and Seattle—collaborated in this study. The study’s participants were approximately 3,500 men who had been diagnosed with primary invasive prostate cancer between October 1994 and October 1995. The group was large, community-based, and included a substantial number of minority and younger men who had been treated in a variety of settings.

PCOS investigators sent questionnaires to participants to obtain information about their urinary, sexual, and bowel functions, plus other quality-of-life issues. Any information on diagnosis or treatment the investigators needed that was not collected by SEER was abstracted from the men’s medical records.

Clinicians and scientists are debating which combinations of treatments (chemotherapy, radiation, surgery, hormonal therapy, and watchful waiting) for clinically localized prostate cancer offer the best chance for long-term survival with the least amount of side effects, particularly long-term urinary and sexual impairments. To help men make more informed choices about treatments that are best for their own situation, PCOS has reported detailed information in numerous research articles about how prostate cancer is treated in this country and the various effects of these treatments on men’s functioning and overall quality of life. Results from PCOS also have been used to assess racial differences in stage at diagnosis and treatment to help explain the significantly higher mortality rates from prostate cancer among black men in the United States.

Selected References


For more information, please see http://healthservices.cancer.gov/pcos/
Breast Cancer Surveillance Consortium

The Breast Cancer Surveillance Consortium (BCSC) is an NCI-sponsored collaborative network of mammography registries with linkages to tumor registries and pathology data. The BCSC was established in 1994 in response to a legislative mandate from the 1992 Mammography Quality Standards Act (MQSA) to evaluate the performance of mammography in community practice and related screening and breast cancer outcomes. Several SEER investigators participate in the Consortium.

At its inception, the objectives of the BCSC were to: (1) enhance the understanding of breast cancer screening practices in the United States and the relationship of these practices to changes in breast cancer mortality or other shorter term outcomes, such as stage at diagnosis or regional survival; (2) foster collaborative research among BCSC participants to examine issues such as regional and health care system differences in the provision of screening services and subsequent diagnostic evaluation; and (3) provide a foundation for the conduct of clinical and basic science research that can improve the understanding of the natural history of breast cancer.

To date, the Consortium has collected data for more than 1.5 million women and 4 million mammograms. Within this group, approximately 34,000 breast cancers have been detected. Thus, the size of the population-based BCSC database, the longitudinal nature of these data, and the multidisciplinary teams of investigators, including radiologists, primary care clinicians, pathologists, epidemiologists, and statisticians, make the BCSC a unique resource for understanding breast cancer screening practices in the United States. More than 150 publications have resulted from the BCSC effort.

Selected References


For more information, see the BCSC Web site: http://breastscreening.cancer.gov/index.html
SEER-Medicare Database

The SEER-Medicare data are the result of linking Medicare-eligible persons with cancer in the SEER data with their Medicare claims. The resulting files provide a unique population-based source of information about health care that spans the continuum of care from the period of initial diagnosis and treatment to long-term followup and care. Investigators using this combined dataset have conducted studies on patterns of care for persons with cancer as well as studies focused on disparities in cancer-related care, use of cancer tests, and the costs of cancer treatment. As of April 2003, more than 100 peer-reviewed publications have used SEER-Medicare data. In the quality-of-care arena, one study examined the use of mammography following a diagnosis of breast cancer and found that, among women treated with breast-conserving surgery without radiation therapy (those most likely to have a recurrence), more than 20 percent had no mammogram in the 2 years following their initial diagnosis. Another analysis demonstrated that men who had radical prostatectomy by surgeons who performed fewer of these procedures were more likely to have late urinary complications than men treated by surgeons who performed the surgery frequently.

The SEER-Medicare database also is a source of data that allows derivation of estimates of cancer-related medical costs by site and stage of disease, by treatment approach, and for each gender in 65 and older age groups. These estimates can be incidence-based, meaning they provide the average cost per patient, or prevalence-based, which provides aggregate expenditures by cancer type. In one study, data on Medicare payments were obtained for colorectal cancer patients for the years 1990-1994 from the SEER-Medicare linked database. Estimates of long-term cost (up to 25 years following the date of diagnosis) were obtained by combining treatment-specific cost estimates with estimates of long-term survival from SEER. The resulting paper demonstrated that valid estimates of cancer-related long-term cost can be obtained from administrative claims data linked to cancer registry data.

Selected References

Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG. Potential for cancer related health services research using a linked Medicare-tumor registry database. Medical Care 1993;31(8):732-748.


More information about the SEER-Medicare data can be found at http://healthservices.cancer.gov/seermedicare/
Health Policy: Colorectal Cancer

Several studies using SEER data have shed light on the use and usefulness of colorectal cancer screening. In 1990, scientists examined the public health impact of mass media coverage of President Reagan’s colon cancer episode of 1985. They found a sharp but somewhat transitory increase in public interest following the diagnosis of the President’s colon cancer, with a corresponding increase in early detection tests. An analysis of the incidence data showed an increase in early stage colorectal cancers in the months following the President’s diagnosis and a decrease in advanced disease in 1986-1987, suggestive of a screening effect.

In 1994, NCI scientists again turned to SEER data as well as national mortality data to examine the abrupt downturn in colorectal mortality rates that began in 1985. SEER data from 1974-1990 revealed for both men and women declining incidence and mortality rates since the mid-1980s, steady declines in distant disease, and increases in local and regional disease until the mid-1980s, followed by declines in the late 1980s. An analysis of mortality rates showed improvements in risk with advancing birth cohorts and more recent time period. This study confirmed the important role of screening to detect early stage cancers for reducing mortality. It also suggested that lifestyle changes observed in younger cohorts have contributed to the lowering of risk.

A study of racial and ethnic patterns in colorectal cancer screening used 1988-1995 data from the California Cancer Registry to compare the cost-effectiveness of two screening interventions. The results showed that average annual age-specific colorectal cancer incidence rates were highest in blacks and lowest in Latinos. Indeed, a 35-year screening program that screened blacks at age 42, whites at 44, or Asians at age 46 would be more cost-effective than screening Latinos at age 50. This study attempted to define more useful cancer screening guidelines and suggested that unique racial/ethnic disease patterns for other cancers also may have implications for screening.

Selected References


Second Cancers

With the increased survival of cancer patients, more than 10 percent of all invasive cancers are second or later primary cancers, making this an important area of concern for patients and their physicians. The large numbers of cancers available from the SEER population-based tumor registries and the long 30-year followup period provide an ideal resource with unique opportunities to study second cancers and add to our understanding of the causes of human cancer. One important area of research has been the late complications of cancer therapy, including second cancers induced by radiotherapy or chemotherapeutic and hormonal agents. In addition, investigators have used SEER data to explore hypotheses on the environmental, genetic, and other causes of increased second cancer risk. Highlights include the following:

• Young women treated with radiotherapy for Hodgkin’s disease (HD) experienced a threefold increased risk of breast cancer, which rose with higher radiation doses to the breast. HD patients treated with radiotherapy had a sixfold risk of lung cancer, with risk related to dose of radiation received.

• Breast cancer patients initially treated with tamoxifen have a twofold increased risk of uterine corpus cancer, with particularly high risks seen for rare tumors of the mixed mullerian type.

• Platinum-based chemotherapy for ovarian cancer increased the risk of leukemia three- to fourfold, and risk rose with increasing cumulative doses to reach eightfold.

• Men with testicular cancer continue to be at significantly increased risk of second malignancies for more than 20 years after treatment.

• Women who received pelvic radiotherapy for cervical cancer were found to have a twofold risk of new cancers in organs that were heavily irradiated.

An NCI Monograph is being prepared to describe the risk of developing a second cancer among nearly 2 million cancer patients reported to SEER.

Selected References


Cancer Prevalence

Cancer prevalence is the number (or percent) of people in a population who are alive on a given date and who previously were diagnosed with cancer. Cancer prevalence is an important estimate of the cancer burden and cancer survivorship in a population.

In the past, cancer prevalence was estimated from the Connecticut tumor registry incidence data. Beginning in 2001, a new methodology was developed using all SEER data to produce cancer prevalence estimates that are more representative of the Nation. Limited duration prevalence (the proportion of people alive at a given date who were diagnosed with cancer during a selected number of years) is estimated using the counting method, which takes into account loss to followup. Estimates of complete prevalence, the proportion of people alive with a history of cancer, are calculated using a statistical method that estimates the proportion of people alive who were diagnosed with cancer before the start of SEER registration.

The cancer prevalence methodology is being disseminated to researchers through the 2003 release of SEER*Stat, which includes the software to calculate limited duration prevalence estimates and its variance. The software is a powerful tool that will enable researchers to calculate prevalence in very flexible ways; for example, for different cancer sites, stages, races, time prior to diagnosis, and different methods for the inclusion of people with multiple tumors.

Further methods are being developed to estimate prevalence of long survivors from childhood cancers.

Selected References


For additional information, please see http://seer.cancer.gov/csr/1973_1999/
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“The SEER program is one of the nation’s true treasures. More than two centuries ago, Thomas Jefferson wrote that it is the responsibility of every American to be informed.’ If Jefferson had been launching an exploration of cancer in America, his Lewis and Clark would have been the SEER Program. It is one thing to talk about the importance of information; it is another to develop and provide the tools and information to enable scientists, planners, advocates, policymakers and all concerned Americans to become informed. Putting timely, accurate, and complete cancer statistics into the hands of citizens with powerful displays and data formats that enable people with different backgrounds to understand them is one of the most important contributions SEER has made.”

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