Cancer Prevention: From 1727 to Milestones of the Past 100 Years

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Abstract

The rich, multidisciplinary history of cancer prevention recounted here begins with surgical and workplace recommendations of the 1700s and ends with 2009 results of the enormous (35,535 men) Selenium and Vitamin E [prostate] Cancer Prevention Trial (SELECT). This history comprises a fascinating array of chemopreventive, vaccine, surgical, and behavioral science research, both preclinical and clinical. Preclinical milestones of cancer prevention include the 1913 and 1916 mouse studies by Lathrop and Loeb of cancer development associated with pregnancy or cancer prevention through castration (oophorectomy), preventing chemically induced mouse carcinogenesis as early as 1929, energy restriction studies in the 1940s, the 1950s discoveries and later molecular characterizations of field cancerization and multistep carcinogenesis, and the effects of angiogenesis inhibition in genetically engineered mice reported in 2009. The extraordinary panoply of clinical research includes numerous large and smaller chemoprevention studies of nutritional supplements, other dietary approaches, a Bacillus Calmette-Guérin trial in 1976, molecular-targeted agents, and agents to prevent infection-related cancers such as hepatitis B virus vaccine to prevent liver cancer in 1984. Clinical surgical prevention includes removal of intraepithelial neoplasia detected by screening (including Pap testing developed in 1929 and vulcoscopy for cervical premalignancy and colonoscopy and polypectomy to prevent colorectal cancer begun in the 1960s) and prophylactic surgeries, such as in Lynch syndrome patients begun in 1977. Behavioral studies include smoking cessation and control beginning in the 1950s, obesity control rooted in studies of 1841, and genetic-counseling and cancer-survivorship studies. This history of pioneering events may help in better understanding who we are and what we want to achieve as cancer prevention researchers and practitioners. [Cancer Res 2009;69(13):5269–84]

Introduction

Cancer prevention generally is considered to be a relatively young field of medicine. In 1727, however, Le Clerc suggested cutting out swellings, polyps, and tumefactions before they became cancerous (1), and in 1775, the English physician Percivall Pott reported a causal link between soot exposure and cancer of the scrotum (later found to be squamous cell carcinoma) in chimney sweeps (2). He subsequently recommended that sweeps, who usually worked naked to avoid soiling their only set of clothes, receive a second set of clothes, not be allowed to sleep naked, and wash after each job (3). Pott’s recommended intervention was not heeded for many years in England, where sweeps continued to suffer a high rate of scrotal cancer, but was implemented in Holland, where scrotal cancer decreased in sweeps. This work made a major contribution to public health policy and prevention in the workplace. Pott’s observational finding was confirmed in 1918 animal studies (4), and scrotal cancer in sweeps was linked to absorption of polycyclic aromatic hydrocarbons in the 1930s (5).

Most if not all of us understand the debt every grant writer owes to “current events” or the most recently published findings supporting the proposed investigation. Likely far fewer investigators appreciate the deep historical roots of every research question posed in a grant. Much of our careers in academic prevention research depends on grants supported in large part by our and others’ publications. And so we write grants and research papers and we survive another day to conduct research. Without our historical forebears and their achievements, however, we would not have a field or form or method to use in advancing the aims of cancer prevention. Seldom blessed with sufficient time to contemplate the full context of our work, perhaps occasionally we should consider that this context as surely includes the steep history of cancer prevention as it does the latest published discoveries on which we attempt to build. The refinement history imposes in winnowing the less important from the important provides a framework for measuring our own professional efforts and directions and thus helps to ensure a robust future for our field.

The following sections will limn many of the historical milestones of cancer prevention in the areas of chemoprevention, vaccines, surgery, and behavioral science. Preclinical milestones range from the first animal prevention studies in 1916 to agent interventions in chemically induced mouse carcinogenesis in 1929 to energy restriction in the 1940s to the discoveries of field carcinization and multi-step carcinogenesis in the 1950s to effects of angiogenesis inhibition in genetically engineered mice reported in 2009. Clinical milestones that have influenced the course of cancer prevention for good or ill range from the Pap test development in 1929 to prophylactic surgeries in the late 1970s to nicotine replacement in the 1980s to cyclooxygenase-2 (COX-2) inhibitor trials, vaccine trials, a molecular-targeted combination chemoprevention trial, and the massive Selenium and Vitamin E Cancer Prevention Trial (SELECT) of recent years.

Chemoprevention

Nutrients and nutrient-related agents. Preclinical and clinical nutrient prevention studies were foreshadowed in 1829 by Récamier, who listed changes in eating habits as a cause of local, acquired or spontaneous, cancers (6). It might be argued that cancer prevention with specific compounds, natural or otherwise, traces its roots back at least 84 years to 1925, when Wolbach [president of the American Association for Cancer Research (AACR) in 1914–1915] and Howe reported that epithelial tissues of rats acquired neoplastic...
properties following the deprivation of fat-soluble vitamin A and that “the study of the reverse changes that follow in the rapid amelioration when the rats are restored to an adequate diet has been begun” (7). Seminal work of the 1950s provided critical support for systemic cancer prevention. Slaughter and colleagues helped clarify carcinogenesis in the oral cavity and other epithelial sites with their report of the concept “field cancerization” in 1953 (8). Based on findings in histologically abnormal tissue surrounding oral cancer, this critical concept postulated that insult from a carcinogen occurs across the entire epithelial field, giving rise to multiple, independent sites of carcinogenesis and thus multiple primary tumors and locally recurrent cancer. The field concept was initially extended to other sites in the aerodigestive tract (9) and ultimately to include virtually every epithelial site. Subsequent molecular findings support this model of carcinogenesis involving field-wide genetically altered cells (10), which explains why successful local control of neoplasia frequently does not prevent second, genetically distinct cancers (or premalignant lesions) in the same epithelial field. The early histologic concept has been updated by molecular biology to include intraepithelial spread of genetically related premalignant clones in the oral cavity (11) and clonal expansion and diversity in the skin, esophagus, and lungs (10, 12). Closely related, equally seminal preclinical work posited the concept of multistep carcinogenesis, stemming from the classic two-step chemical carcinogenesis model introduced in 1938 (13). In 1954, Auerbach began (in the lung) some of the first detailed histologic studies of multistep progression (from hyperplasia to metaplasia to dysplasia to carcinoma in situ to cancer), which correlated with intensity of smoking (14). In 1976, Weinstein (AACR president in 1990–1991) and collaborators reported key early studies of the carcinogen benz(a)pyrene that led to the broad study of DNA adducts in polycyclic hydrocarbons and other carcinogens such as aflatoxins (15–18). The probable date of the first elucidation of molecular events in the multistep process was 1988, when Vogelstein observed these events and steps in preinvasive colorectal carcinogenesis (19). Sidransky and other investigators quickly extended this molecular work to oral and other sites of epithelial neoplasia (20).

In 1966, Wattenberg (AACR president in 1992–1993) introduced the term “chemoprophylaxis” in a landmark review of experimental inhibition of chemically induced animal carcinogenesis that appeared in the AACR journal Cancer Research (21). He surveyed “a scattered group” of his and other groups’ prevention-related animal studies ranging from 1929 (the inhibitory effects of mustard gas on tar-induced skin carcinogenesis; ref. 22) to 1965 (e.g., preventive effects of phenothiazines, their derivatives flavone and benzoflavone, and actinomycin D; refs. 23–25), stating that “a major purpose of this review is to stimulate further work on the chemical inhibition of chemical carcinogenesis since this area of research appears to have considerable potential for yielding information of fundamental importance and conceivably might eventually have some applied aspects.” This review included summaries of early mechanistic studies of Conney (26) involving preventive agent effects in inducing phase I and phase II enzymes that inhibit carcinogenesis. Talalay helped extend this work in late-1970s studies he called “chemoprotection” (27, 28), linking basic molecular studies with preventive effects of the food preservatives butylated hydroxyanisole and butylated hydroxytoluene and dietary approaches involving vegetables such as broccoli.

Picking up the thread of vitamin A research where Wolbach and Howe (7) and a few subsequent investigators left off (29, 30), Bollag began a program in 1967 to synthesize the first analogues of vitamin A, later coined “retinoids” by Sporn (31, 32). He hypothesized that these analogues not only would enhance potential therapeutic and preventive effects of natural vitamin A but also would reduce its well-known severe toxicity (hypervitaminosis A). As long ago as 1597, European Arctic explorers reported developing life-threatening vitamin A poisoning from eating polar bear liver (an effect long known to the Inuit), and Antarctic explorers suffered the same consequences in 1913 after eating the livers of sled dogs (33, 34). The Bollag, Moon, and Sporn groups conducted the first preclinical prevention studies of synthesized retinoids in the 1970s (32, 35, 36), and in 1976, Sporn corroborated the generic applicability of this entire approach and introduced the commonly used modern term “chemoprevention” for describing it (32). In the late 1970s and early 1980s, pilot clinical trials of natural and synthetic retinoids were conducted in patients with oral leukoplakia including that caused by betel nut chewing in India, Philippines, Taiwan, Guam, and Russia. Alberts, Meyskens, and colleagues conducted a series of clinical retinoid prevention trials in various sites. Beginning in 1982, they reported phase I and phase II trials of topical all-trans retinoic acid (RA) for cervical dysplasia, culminating in their 1994 phase III randomized controlled trial (RCT; ref. 37), which found significant activity in moderate, but not severe, cervical dysplasia. Two other notable early clinical retinoid trials involved skin cancer prevention: high-dose 13-cis-RA in high-risk xeroderma pigmentosum patients (38) and retinol in moderate-risk patients (39).

Hong (AACR president in 2001–2002) and colleagues developed the first fully realized program of translational retinoid prevention research, which focused on head and neck and lung carcinogenesis. Although this program was not translated into standard of care, it was instrumental in providing the methods for later translational research into molecular-targeted chemoprevention. Begun in 1982, their RCT of a high-dose retinoid showed the promise of this agent class for oral cancer prevention (40). In 1983, they began a trial that later demonstrated the proof of principle of chemoprevention in showing that an adjuvant high dose of the retinoid 13-cis-RA prevented second primary tumors in patients with curatively treated stage I–IV head and neck cancer (41). Although active, high-dose 13-cis-RA was too toxic and reversible for sustained oral cancer prevention, and lower, more tolerable doses did not translate into long-term head and neck cancer risk reduction. For example, lower-dose 13-cis-RA did not prevent head and neck cancer–related second primary tumors or recurrence in a definitive large-scale trial reported in 2006 (42); the similar Lung Intergroup Trial to prevent lung cancer–related second primary tumors or recurrence also did not achieve a positive result (43). Helping to pioneer modern methods of translational biomarker research, this group integrated adjunctive analyses of biomarkers including RA receptors (RAR), p53, loss of heterozygosity (LOH), and cyclin D1 within their extensive 20-plus-year program of clinical retinoid trials in patients with oral carcinogenesis (44–48). A major achievement of this translational work was the finding of Lotan and colleagues that RAR-β expression was suppressed in oral leukoplakia and up-regulated by a retinoid (49) in another trial of this group (50). This RAR-β finding was a translation of the discovery of the nuclear RARs beginning with the seminal codiscovery of the first RAR by Chambon (51) and Evans (52) in 1987.

The U.S. National Cancer Institute (NCI) founded the Division of Cancer Prevention and Control (later shortened to Division of Cancer Prevention) in 1983 and conducted the first large clinical
Chemoprevention workshop in 1984 (53). The record of NCI-sponsored nutrient trials with noncancer end points includes an important 1990s trial of calcium that reduced adenoma risk by a modest statistically significant 19% (54). Clinical chemoprevention studies with a cancer end point began to be launched in 1985, frequently involved nutritional supplements, and have been largely negative-neutral and some even harmful (55). The first two such trials, the Alpha-Tocopherol and Beta-Carotene (ATBC) trial (56) and Beta-Carotene and Retinol Efficacy Trial (CARET; ref. 57), provided a stunning reversal for the field when they found that the nutrient β-carotene increased lung cancer risk in smokers, the major at-risk population. A high-profile epidemiology review of 1981 supported these and other β-carotene RCTs (58–60). Two other important negative nutrient-related cancer end point trials were the adjuvant Lung Intergroup Trial and head-and-neck trial of low-dose 13-cis-RA (42, 43). Perhaps the capstone on the long series of definitive large-scale nutrient trials was the negative-neutral Selenium and Vitamin E [prostate] Cancer Prevention Trial (SELECT) in 35,335 men (61, 62), which led to the widely held view that “the prospects for cancer prevention through micronutrient supplementation have never looked worse” (63). SELECT arose, in part, from a suggestive RCT finding that combined β-carotene, α-tocopherol, and selenium was associated with total and gastric cancer mortality reductions (versus participants not receiving this combination) in the high-risk area of Linxian, China (64), and, in larger part, from secondary findings of prostate cancer prevention in the earlier ATBC trial and Nutritional Prevention of Cancer (NPC) Study of selenized yeast, which was negative in its primary end point (skin cancer prevention; ref. 65). Epidemiologic cohort studies had supported trials of micronutrients for cancer prevention, but reducing these findings to specific nutrients did not generally work in clinical RCTs, suggesting roles for several factors, including relative macronutrient density and complex mixtures of bioactive compounds (not limited to micronutrients), only in any potential benefit of foods in reducing cancer risk. Another speculation is that specific supplements may be effective only in a population deficient in that nutrient, exemplified perhaps by the contrasting effects in the generally selenium-deficient NPC population and replete SELECT population (62, 63).

Early reports of the related study of interventions with whole food products or food extracts as single compounds or in complex mixtures include a 1987 report on green tea polyphenols (66), a 1988 report on curcumin by the Conney group (67), a 1997 report on resveratrol (68), and recent reports on deguelin (69) and myoinositol (70), which has moved into clinical testing in the lung with promising results (71). An emerging area of great importance for interventions with natural compounds is nutrigenetics for identifying the populations most likely to benefit from specific compounds (72, 73).

**Molecular-targeted agents.** A rich history of preclinical molecular-targeted research gave rise to exciting clinical advances of cancer prevention. In 1896, Beatson presaged molecular-targeted hormonal prevention of breast cancer by observing that oophorectomy had a beneficial effect on advanced breast cancer (74). In 1932–33, Lacassagne reported that estrogen could induce mammary tumors in mice and speculated that estrogen antagonism (which did not exist at the time) may prevent breast cancer (75, 76). The estrogen receptor was discovered in 1966 (77), and in 1974, Jordan showed that the selective estrogen receptor modulator (SERM) tamoxifen prevented mammary tumors in rats (78). In 1941, Huggins (AACR president in 1948–1949) presaged molecular-targeted hormonal prevention of prostate cancer in a report published by Cancer Research showing that castration had a beneficial effect on metastatic prostate cancer (79), receiving a 1966 Nobel Prize in Physiology or Medicine related to this work. Clinical COX-2 targeting in familial adenomatous polyposis (FAP) and sporadic colorectal adenoma patients was based in part on two important laboratory advances. DuBois (AACR president in 2008–2009) and colleagues showed in 1994 that COX-2 is up-regulated in human colorectal adenomas and adenocarcinomas (80), and Taketo and colleagues showed in 1996 that COX-2 targeting was effective against intestinal neoplasia in adenomatous polyposis coli (Apc) knockout mice (81).

Although not yet translated into clinical prevention trials, seminal transgenic mouse studies reported by Folkman, Hanahan, and colleagues in 1989 and 1996 contributed the “angiogenic switch” (82, 83). Antiangiogenic agents were shown in 1999 to have a spectrum of chemopreventive to late-treatment effects on transgenic mouse-model carcinogenesis (84). Seminal work on epigenetic phenomena includes mechanistic studies by Jones (AACR president in 2005–2006) and colleagues showing that DNA methylation contributes to human carcinogenesis (85); these studies are among the first to show that methylation in premalignant lesions is important in the development of chemically induced cancer in rodents (86). In 1983, Vogelstein reported early cancer-related epigenetics data showing that hypomethylation occurs in premalignancy (87). In 1994, investigators reported the first systematic study of methylation as a very early event of human colorectal neoplasia (88), and in 1995, investigators showed that targeting to reverse methylation can prevent intestinal neoplasia in mice (89).

The 1998 report of the watershed Breast Cancer Prevention Trial (BCPT) represented a turning point in the negative course of cancer end point trials. The SERM tamoxifen reduced breast cancer risk by 50% in BCPT (90), leading to a U.S. Food and Drug Administration (FDA) approval of tamoxifen in this setting and for contralateral breast cancer prevention in the same year. Ford of the NCI and Fisher were instrumental in developing the breast cancer prevention RCTs (91). Subsequent positive molecular-targeted trials included one of celecoxib in FAP patients (92; ref. 93) leading to an FDA approval in 1999), the Prostate Cancer Prevention Trial (PCPT) of finasteride (93), and the Study of Tamoxifen and Raloxifene (STAR; ref. 94; leading to an FDA approval of the SERM raloxifene in 2007). First reported in the late 1980s (95), adjuvant activity of tamoxifen in preventing contralateral breast cancer provided substantial support for implementing the series of SERM trials including BCPT, International Breast Cancer Intervention Study (IBIS) I (tamoxifen versus placebo; refs. 96, 97) and IBIS II (ongoing trial of tamoxifen versus anastrozole, an aromatase inhibitor), and STAR. Long-term follow-up of IBIS I showed that the benefits of tamoxifen persisted for, and most of the worrisome toxic effects wore off within, 10 years (or 5 years after tamoxifen treatment stopped).

Reported in 2003, the other major advance with molecular-targeted hormonal cancer prevention was the large-scale PCPT of the 5α-reductase inhibitor (type 2) finasteride, which blocks production of potently carcinogenic dihydrotestosterone (93). Although finasteride significantly reduced prostate cancer risk in PCPT, its acceptance for this use has been blocked by concerns that finasteride increased high-grade prostate cancer and only prevented clinically insignificant disease. New PCPT analyses reported in 2007–2008 indicated that finasteride prevented clinically
meaningful disease and did not increase aggressive disease; these
data may eventually overcome the obstacles to the acceptance of
finasteride for prostate cancer prevention (98–102). Reported in
2009, the related Reduction by Dutasteride of Prostate Cancer
Events (REDUCE) trial of the dual (type 1 and type 2) 5α-reductase
inhibitor dutasteride found that prostate cancer risk went down by
23% and high-grade prostate cancer did not increase significantly
(versus placebo) in a higher-risk group (e.g., elevated prostate-
specific antigen, albeit with a prior negative biopsy) than that of
PCPT (103). These results confirm a class effect of 5α-reductase
inhibitors and have important regulatory implications for prostate
cancer prevention.

Reported in 1993, an RCT of the nonsteroidal anti-inflammatory
drug (NSAID) sulindac showed the first substantial chemopreventive
effects in the setting of colorectal adenomas (104). A subsequent
RCT of the COX-2-selective NSAID celecoxib reduced polyps in FAP
patients (92) and led to the U.S. FDA approval of celecoxib as an
adjunct to other standard care for FAP patients. Aspirin has
significantly reduced the risk of adenomas (especially advanced
adenomas, reduced by ~30%) in several well-designed RCTs (105,
106) and has significantly reduced colorectal cancer risk in pooled
analyses of cardiovascular protection RCTs (26% reduction; ref. 107);
note, high-dose aspirin selectively prevented COX-2-expressing
colorectal cancer (108). The randomized, controlled Adenomatous
Polyposis Prevention on Vioxx (APPROVe), Adenoma Prevention
with Celecoxib (APC), and Prevention of Colorectal Sporadic Adenoma-
tous Polyps (PreSAP) trials assessed COX-2-selective NSAIDs for
reducing sporadic colorectal polyps. Drug administration in these
RCTs was stopped early because interim analyses of the APPROVe
and APC trials indicated unexpected increases in cardiovascular
event rates, although such was not the case in the PreSAP trial (109–
111). Initial analyses of serious cardiovascular adverse events in the
APC trial indicated dose dependency and a higher cardiovascular
risk associated with a previous history of cardiovascular disease.
Subsequently published reports indicated that each of these trials
achieved significant reductions in colorectal adenomas (110, 112,
113). A pooled analysis of the major celecoxib RCTs in nonarthritis
settings found that people with a low baseline cardiovascular risk
seemed to have no increase in serious cardiovascular events at
celecoxib doses up to 400 mg twice a day (114). The final planned
APC analysis found that a history of atherosclerotic heart disease
was the only specific risk factor that interacted significantly with
celecoxib in producing adverse cardiovascular events (115). Recent
APC data also suggest that certain germ-line genetic changes may be
especially sensitive to celecoxib for colorectal adenoma
prevention (116).

A recent landmark trial of combination chemoprevention found
that difluoromethylornithine (DFMO) and sulindac reduced
overall colorectal adenoma recurrence by 70% and advanced
and/or multiple adenomas by more than 90% (117). This trial built
directly on a 1986 preclinical study of DFMO and an NSAID (118)
and provided the first clinical validation of the important direction
of molecular-targeted combinations rooted in proposals of Sporn
in 1980 (119, 120).

**Prevention with Vaccines and Other Nonnutrient, Non–Molecular-Targeted Agents**

Bacillus Calmette-Guérin (BCG) for preventing recurrence of
superficial tumors of the bladder traces its roots back to the ob-
servation of Coley in 1893 that toxic bacterial products could have
a role in cancer therapy (121). About the same time, other studies
suggested a lower frequency of cancer in tuberculosis patients
(122), a concept reinforced in 1929 by a necropsy series of Pearl
(123). BCG was developed as a tuberculosis vaccine in 1908 at the
Pasteur Institute of Lille, and its first use against tuberculosis in
humans came in 1921. The first published report of BCG as a
cancer vaccine (in Swedish patients) came out in 1935, and experi-
mental and clinical studies of the late 1950s and 1960s generated
enthusiasm for BCG in various cancers (122). In 1976, when stan-
dard therapy of superficial (noninvasive) bladder cancer was radi-
cal cystectomy, Morales and colleagues first described BCG in this
setting (124) and followed up with a positive phase II trial (125).
The FDA approved BCG for preventing recurrence of superficial
bladder cancer in 1990 based on several clinical trials including one
by the Southwest Oncology Group (126). In 1998, the FDA
approved valrubicin for preventing BCG-refractory superficial bladder
tumor recurrence (127).

A national program to vaccinate children against hepatitis B (a
major risk factor for liver cancer) was implemented in Taiwan in
1984, substantially lowering liver cancer risk (128); hepatitis B
vaccination also reduces risk (129). Blumberg had discovered the
hepatitis B virus in 1967 (130) and its link with hepatocellular
carcinoma in 1975 (131), winning a Nobel Prize in Physiology or
Medicine for this work in 1976, the same year that the hepatitis B
vaccine was developed. Another infection-related landmark of
cancer chemoprevention involves human papillomavirus (HPV),
which was discovered in 1907 (132). zur Hausen reported the link
between HPV infection and cervical cancer in 1974 (133) and
discovered the first specific human HPV (type 16) in cervical cancer
patients in 1983 (134), leading to an RCT of an HPV-16 vaccine
(135) developed by Lowy, Schiller, and others (136) and then to
RCTs begun in 1991 to test quadrivalent and bivalent HPV vac-
cination for preventing cervical cancer in girls and young women
(137–139). In 2006, the U.S. FDA approved quadrivalent HPV vacci-
nation for girls and young women ages 9 to 26 years for preventing
cervical cancer, cervical adenocarcinoma in situ, and high-grade
cervical, vulvar, and vaginal intraepithelial neoplasia (IEN), and an
application for FDA approval of bivalent HPV vaccination for
cancer-risk-reduction is ongoing, zur Hausen was recognized for
his work in this area by a 2008 Nobel Prize in Medicine, and
HPV now is also clearly linked to oropharyngeal cancer develop-
ment (140).

*Helicobacter pylori* illustrates the complexity of controlling
microbe-related cancers (141). Recognition of *H. pylori* as the
major worldwide cause of stomach cancer followed the 1989 and
1991 discovery by Blaser and others of its link with gastric
neoplasia (142–144). In 1997, an inverse association between *H.
 pylori* and gastroesophageal junction adenocarcinoma was
reported (145), and while *H. pylori* eradication has reduced
stomach cancer, it also may be increasing esophageal adenocar-
cinoma. *H. pylori* increases noncardia gastric cancer and protects
against esophageal and cardia gastric cancers (146), and 1989 data
showed that *cag A* + *H. pylori* is the strain with the strongest risk of
gastric cancer and strongest protective effect against esophageal
cancer (147, 148). *H. pylori* eradication recently reduced the oc-
currence of metachronous gastric cancer in patients resected for
early gastric cancer (149). In 2005, Marshall and Warren were
recognized with a Nobel Prize for their discovery of *H. pylori* and its
link with duodenal and gastric diseases (150).

Oral contraceptive pills reduced the risk of ovarian cancer by
about 40% in multicenter, population-based, case-control studies.
Surgical Prevention

Prophylactic surgery. Along with screening-associated surgery for premalignant conditions (discussed later), the other major surgical approach is prophylactic surgery in high-risk people with heritable (germ-line) genetic disorders. Foreshadowing both surgical approaches in 1829, Récamier wrote that "constitutional" cancers can be hereditary and that the cause of local (acquired or spontaneous) cancers can be due to degeneration of preexisting benign lesions (e.g., pigmented nevi and polyps; ref. 6). Two preclinical studies reported in 1913 and 1916 by Abbie Lathrop and Leo Loeb (AACR president in 1911–1912) examined cancer development associated with pregnancy (156) or cancer prevention through castration (oophorectomy; ref. 157) in female mice. The 1916 article (157) was published in the first year of the first AACR journal, The Journal of Cancer Research, renamed American Journal of Cancer in 1931 and Cancer Research in 1941. This article states that "the present contribution is intended as the first in which...we seek...to inquire into possible means of preventing the spontaneous development of malignant tumors in mice. Further investigations in this direction have been begun," reflecting the possible historical first examination of preclinical cancer prevention, 140 years after the observational and interventional contributions of Percivall Pott in humans (3).

Cancer prevention through prophylactic, organ-removing surgery traces its roots back to 1895, when Alfred Scott Warthin (AACR president in 1927–1928) began observing "family G," which had an unusually high intergenerational prevalence of cancer (158). These human observations were echoed by Maud Syle in a 1916 article on "inheritable" cancers in mice (159), which appeared in the same issue of the journal that published the 1916 Lathrop and Loeb article discussed above (157). Colectomy for "familial polyposis of the colon" was reported as early as 1901 and seems to have become standard colorectal cancer prevention by no later than 1948 (160, 161) in this setting. The cancer history of family G was updated by Warthin in 1925 (162), by Weller and Hauser in 1936 (163), and by Lynch in 1971 (164). In 1977, Lynch first recommended prophylactic, organ-removing surgery based on his studies of heritable cancers (165). Originally called Cancer Family Syndrome, a high familial prevalence of colon and endometrial cancer is now called hereditary nonpolyposis colorectal cancer syndrome, or Lynch syndrome. Lynch's early recommendations included total colectomy for initial colorectal cancer in an extremely high-risk relative, as opposed to hemicolecotony, and "total prophylactic colectomy in colon cancer patients of kindreds manifesting the Cancer Family Syndrome." He also recommended that female colorectal cancer patients from such families who have completed childbearing should consider prophylactic hysterectomy at the time of colon surgery. He further suggested that endometrial carcinoma patients from such enormously high-risk families should consider total prophylactic colectomy (165). He also advocated prophylactic mastectomy and prophylactic oophorectomy in women at extremely high cancer risk due to hereditary breast cancer and hereditary breast-ovarian cancer syndrome (165–168). These recommendations included prophylactic contralateral mastectomy for these patients who developed breast cancer and prophylactic bilateral oophorectomy for highly selected candidates with ovarian cancer risks approaching 50%.

The study of childhood cancers shed early light on cancer genetics, showing that retinoblastoma has an inherited susceptibility and thus at least one "genetic" event. Knudson developed the "two-hit model" for retinoblastoma in 1971 (169), and this model was extended to Wilms' tumor and neuroblastoma by Strong (AACR president in 1996–1997) in 1972 (170, 171). These studies led to the concepts and discoveries of relevant tumor suppressor genes and tumor-specific LOH. The characterization of Li-Fraumeni syndrome resulted from family studies of childhood cancer patients and their risks for second tumors; Li-Fraumeni is a rare inherited syndrome attributable to germ-line mutations in the tumor suppressor gene TP53 and comprising multiple primary sarcomas, breast cancer, brain tumors, adrenal cortical tumors, and a variety of other cancers (172, 173). The study of rare childhood cancer syndromes has advanced our understanding of molecular mechanisms not only of heritable cancer (174) but also of tumorigenesis in general.

Dating from 1987, molecular articles that identified the germ-line changes (e.g., mismatch repair genes including MSH2) responsible for hereditary nonpolyposis colorectal cancer, or Lynch syndrome, have validated the experiential observations of Lynch and his predecessors (175–182). Nearly 30 years after the first recommendations for prophylactic surgery, results of large studies confirmed the hypothesized reductions in cancer risk from removal of the fallopian tubes and ovaries for hereditary breast-ovarian cancer (183, 184) and from removal of the uterus and ovaries for Lynch syndrome (185). Tubal ligation has also been shown to reduce ovarian cancer risk (153). In addition, large observational cohort studies demonstrated that prophylactic mastectomy in women at risk of familial breast cancer (186), including BRCA1 or BRCA2 mutation carriers (187), substantially reduced the risk of breast cancer. These studies have validated Lynch's early recommendations, and surgical prevention plays an important role in the management of individuals with hereditary cancer syndromes (188).

Screening and resection of preinvasive neoplasia. The second major area of surgical prevention is screening-associated surgery for premalignant lesions. In 1928, Papanicolaou published results of his study of normal and malignant cytology in vaginal samples of cells shed from the cervix, vagina and endometrium in humans (189). A newspaper article of the day stated, "Although Dr. Papanicolaou is not willing to predict how useful the new method will be in the actual treatment of malignancy itself, it seems probable that it will prove valuable in determining cancer in the early stages...even...precancerous conditions may be detected and checked." Named after him, the Pap test was validated as a diagnostic tool in 1943 (190) and introduced in the United States in the late 1940s to early 1950s, and the NC1-sponsored Bethesda System of 1988 (191) is one of several subsequent refinements of the Pap test and its interpretation. Pap screening primarily detects cervical neoplasia but can detect neoplasia of the vagina (which is rare) and endometrium (for which the test is insensitive) as well. Although standard and widely used, Pap screening, culposcopy, and removal of cervical IEN to reduce the incidence and mortality of cervical cancer has never been tested in a randomized trial. The
informative early studies of this approach were observational case-control studies (192), the best of which were Nordic studies finding decreased cervical cancer mortality after Pap screening was introduced (193, 194). These studies have been confirmed empirically by a long-term decline in cervical cancer mortality since Pap testing and cervical IEN removal began, although other factors including hysterectomy also figure into this decline. Ranging from 8% to 73%, the mortality reduction between the pre-Pap period of 1963–1967 and post-pap period of 1978–1982 was lowest (8%) in the lowest-Pap-participation group in Norway and highest (73%) in Iceland, where Pap participation was very high. Approximately 200 years after Pott, these data resonate of the England versus Holland findings on cancer prevention in chimney sweeps (3). The study of HPV in cervical cancer etiology and prevention has led to the advance of HPV detection in screening and surgical prevention in the cervix (195).

Leborgne classified breast microcancer in 1950 (196, 197), followed by the first equipment dedicated to mammography in 1956. By the early 1980s, the widespread use of screening mammography had dramatically increased the detection of ductal carcinoma in situ (DCIS), spotlighting cancer prevention in this setting. At that time, DCIS treatment ranged from local incision with or without radiation to unilateral to bilateral mastectomy. By 1985, mastectomy was little justified and lumpectomy more common for invasive breast cancer (198), but mastectomy was still common in cases of DCIS. Fisher and colleagues of the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated a trial in 1985 to compare effectiveness between the less morbid DCIS treatment options (199), finding that lumpectomy followed by radiotherapy was more effective than was lumpectomy alone. They followed up with the finding that tamoxifen plus lumpectomy and radiation was better than lumpectomy and radiation for preventing cancer in DCIS patients (199). These trials established lumpectomy plus radiation plus tamoxifen as standard of care for DCIS patients.

Colorectal screening and polypectomy began in the 1960s (200–202) and became standard practice even before they were established for preventing colorectal cancer by observational studies including the National Polyp Study (203). This study began in 1980, was reported in 1993, and showed up to 90% reductions in colorectal cancer incidence among subjects undergoing regular colonoscopic surveillance and polypectomy for adenomas (compared with incidences in three historical control groups—two cohorts without regular surveillance/polypectomy and one cohort from a general population registry). In 1995, colonoscopic screening and polypectomy were shown to effectively reduce colorectal cancer risk in Lynch syndrome (hereditary nonpolyposis colorectal cancer) patients (204). Observational and clinical studies confirmed significant reductions in colorectal cancer mortality and, in some cases, incidence in the context of colorectal screening by stool blood–based tests or flexible sigmoidoscopy combined with colonoscopic adenomectomy (201, 205).

Behavioral Prevention

Smoking cessation and control. Reports of smoking various materials including cow dung as treatment for melancholia date back to Herodotus in the 5th century BCE (206). Tobacco is native to the Americas, however, and smoking tobacco began with native peoples of the New World long before it was known to Europeans, who adopted the custom as sailors began bringing tobacco plants home with them in the decades after Columbus discovered Cuba and Hispaniola in 1492. Smoking tobacco grew in the New World European colonies and, subsequently, in the United States as well, reaching a prevalence of 65% cigarette smoking in 1940 among U.S. men born in 1911–1920, staying near this level for like-aged men (20–30 years old) until 1955, and generally declining since then; the prevalence among women began to increase in the 1930s and peaked at 38% in 1960, when it too began to decline, although less so than among men (207).

There is no better example of the important link between cancer prevention and cancer epidemiology than that reflected by lung cancer risk and its smoking-related epidemiology beginning as early as the 1700s (208). Seminal epidemiologic studies of Wynder and Doll fully demonstrated the long-suspected association between cigarette smoking and lung cancer risk in 1950 (209, 210). The U.S. Surgeon General’s Report of 1964 (211) established this association by adding the data of Auerbach showing the causal relationship between smoking and neoplasia in lung tissue to the compelling 1950 and later epidemiologic evidence, thus prompting major policy changes, media campaigns, cigarette taxation, and other measures to combat cigarette smoking, including the 1965 Federal Cigarette Labeling and Advertising Act requiring printing of warnings on cigarette packs and the 1970 U.S. Public Health Cigarette Smoking Act banning advertising for cigarettes. Important tobacco biology studies of 1978 identified tobacco-specific nitrosamines (212). After peaking for men in 1955 and for women in 1960, the overall U.S. cigarette smoking rate was down to 41.9% (age adjusted; 51.2% male, 33.7% female) by 1965, one year after the Surgeon General’s historic report; the 1965 rate for young people ages 18 to 24 years was 42.4% (51.9% male, 33.9% female; refs. 213, 214). Beginning in the 1970s, antismoking regulations included nonsmoking areas in public places and, most important, the smoke-free workplace, which has had the biggest impact on smoking control; the overall age-adjusted U.S. smoking rate by 1979 was 33.3%.

Studies of the addictive nature of tobacco use began in the early 1900s (215), and studies of the biology of carcinogenesis induced by the numerous carcinogens in tobacco smoke seem to date back at least to the early 1950s (216–218). The scientific name of tobacco is Nicotiana, and 1970s research focused on the addictive component nicotine, examining its dependency-producing effects, pharmacokinetics, pharmacodynamics, self-administration, withdrawal, and tolerance (215, 219). The early 1990s suggestion of a genetic influence underlying tobacco dependence comes from several lines of research including twin studies and studies of the association between germ-line gene variants in neurotransmitter systems and tobacco dependence (220, 221), including germ-line variation studied by molecular epidemiology pioneer Spitz and colleagues and others in dopamine receptor genes (222). The first nicotine replacement pharmacotherapy was nicotine gum (219, 223), which the U.S. FDA approved in 1984; the FDA now has approved three classes of smoking-control agents: nicotine replacement (e.g., in gum and patches); bupropion antidepressant products; and varenicline, a nicotinic acetylcholine partial agonist (224). Two large, important NCI-sponsored antismoking studies with positive but limited results were the clinical Community Intervention Trial for Smoking Cessation (COMM; launched in 1988; refs. 225, 226)
and the policy-driven American Stop Smoking Intervention Study (ASSIST; implemented from 1993 through 1999; ref. 227). The first pharmacogenetic studies were reported in 2002 (228, 229). Historically, the impact of behavioral trials on smoking behavior has been less than that of public policy measures, although many experts believe that clinical trials in targeted populations should play a bigger role going forward. As of 1995, the overall age-adjusted U.S. smoking rate in people 18 years and older was 24.8%.

In the 1970s, Peto advanced the understanding of worldwide tobacco-related mortality, predicting 1 billion avoidable deaths in the 20th century if then-current smoking patterns persisted and (with Doll) showing in 1976 that half of all persistent smokers eventually die of their habit and can reduce this risk by quitting smoking (230, 231). These investigators further elucidated the avoidable causes of cancer, including smoking and dietary factors, in a landmark epidemiologic review published in 1981 (232). With a weaker effect, second-hand smoke exposure was more difficult to establish in causing lung cancer than was smoking. The 1992 Environmental Protection Agency report “Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders” concluded that “environmental tobacco smoke [ETS (or second-hand smoke)] is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers” (233). This conclusion met with substantial skepticism because the epidemiologic data were somewhat limited and lung carcinogen metabolites were not yet reported in exposed nonsmokers. Then in 1993, Hecht and colleagues published the first report establishing the presence of 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone and 4-(methyl)nitrosamino)-1-(3-pyridyl)-1-butanol-glucuronide, metabolites of the potent tobacco carcinogen 4-(methyl)nitrosamino)-1-(3-pyridyl)-1-butane, in the urine of nonsmokers exposed to second-hand smoke (234). This group followed with a series of studies firmly establishing the presence of these lung carcinogen metabolites in the urine of infants, elementary school children, women living with smokers, casino patrons, and restaurant and bar workers (reviewed in ref. 235). The metabolites were not detected in nonexposed people. The epidemiologic data also evolved, and by the time of the 2004 International Agency for Research on Cancer (IARC) Monograph “Tobacco Smoke and Involuntary Smoking” (236) and the 2006 U.S. Surgeon General’s Report “The Health Consequences of Involuntary Exposure to Tobacco Smoke” (237), all doubt that second-hand smoke causes lung cancer was erased. The link between second-hand smoke and lung cancer has spurred or strengthened legislation in many states to protect nonsmokers in workplaces, bars, and restaurants. Regulation of indoor smoking reduces smoking cues and amounts, ultimately will change social norms, and therefore has become a pillar of tobacco control, along with aggressive counteradvertising and taxation, which are effective in decreasing smoking prevalence (238).

Gritz advanced our understanding of cigarette smoking behavior in women and other special populations, addressing, for example, smoking initiation and smoking cessation in the seminal 1980 U.S. Surgeon General’s report entitled The Health Consequences of Smoking for Women (239). Important disparities in smoking behavior and health consequences among people with a lower versus a higher socioeconomic status have been studied since the mid-1990s (240). Smoking behavior and smoking-related health consequences are becoming increasingly concentrated within low socioeconomic status individuals (240–244), leading to initiatives in this group to eliminate barriers and increase access to smoking cessation and control programs (245–249), as recommended in the “evidence-based tobacco control strategies” proposed in Making Cancer Health Disparities History: Report of the Trans-HSS Cancer Health Disparities Progress Review Group, 2004.

First published in 1996 and updated most recently in 2008, the clinical practice guideline Treating Tobacco Use and Dependence of the U.S. Department of Health and Human Services presents state-of-the-art evidence for and meta-analyses of treating tobacco use with behavioral or pharmacologic approaches or both (224, 250). An important commentary of 2006 observed that the reversal in total U.S. cancer deaths in the late 1990s was driven largely by a reduction in male lung cancer resulting from the beneficial effect of 30 years of declining smoking rates (251). An important monograph of 2007 outlined an innovative strategic plan “for intensifying and accelerating public health efforts, thereby taking long strides toward ending the tobacco problem in the United States” (252). Following historic U.S. court decisions holding tobacco companies financially responsible for the health consequences of cigarette smoking, the Tobacco Master Settlement Agreement (MSA) was struck between the major tobacco companies and 46 states, the District of Columbia, and the U.S. territories in 1998 (252). The MSA imposes certain restrictions on practices by the companies and requires them to pay compensation to the states for health costs of patients with smoking-related illnesses. On the other side, the states agreed to settle existing litigation against the companies, and the companies received general protection from future law suits over harm from tobacco use. This is the largest civil settlement in U.S. history, requiring the companies to pay an estimated $206 billion between 2000 and 2025. The MSA also created the nonprofit American Legacy Foundation (ALF) for the purpose of reducing teenage smoking and preventing tobacco-related diseases. Most ALF funding ended after 5 years, however, because its continuance depended on the companies who signed the MSA maintaining at least a 99.05% market share. The signature accomplishment of ALF is the Truth public-health campaign, which was credited in 2005 with a 22% decline in youth-aged smoking (253). As of 2006, the overall age-adjusted U.S. smoking rate in people 18 years and older was 20.8%, half the 41.9% rate of 1965.

Screening utilization and genetic counseling measures. An important early step in the development of behavioral science methods for prevention and screening interventions was the Yale Conference on Behavioral Medicine held in 1977 (254, 255). Behavioral approaches (involving individual-level factors such as age, education level, preferences, and broader environmental factors, e.g., access to care) to increase screening utilization in the healthy general population stemmed from the introduction of mammography screening for early treatable preinvasive or invasive breast cancer and subsequent screening for skin, colorectal, and prostate neoplasia (256–258). Behavioral approaches among high-risk women to treat the anxiety caused by, and help in understanding the health and social impact of, genetic testing followed the identification of genetic markers of familial, heritable cancers especially of the breast and ovary (259).

Psychosocial research in the area of genetic testing for cancer risk is designed to improve cancer prevention (through risk-reducing surgery or chemoprevention) and early detection (through targeted surveillance and screening) in high inherited risk populations. In 1982, Kessler first defined a psychological
Prior to the availability of clinical genetic testing, several important studies published in 1992–1993 established that women who had close relatives with breast cancer were themselves at risk for increased psychological distress (261–263). Therefore, when clinical genetic testing for hereditary cancer risk first became available, a primary concern was adverse psychological consequences due to counseling and testing. The first two studies to identify how people respond to results of testing, BRCA1/BRCA2 testing in this case, were reported in 1996–1997 by Lerman and others (264, 265), finding that people with no personal history of cancer and a positive test result had the greater risk of psychological distress and that people with a negative result experienced a psychological benefit. Other notable advances include identifying the importance of informed consent for cancer genetic testing (266) and the importance of addressing both the educational and psychosocial needs of individuals undergoing counseling (267). The first studies shedding light on how genetic testing influences the adoption of risk management behaviors (268, 269) found that notification of positive mutation carrier status can improve uptake of screening recommendations for breast and colorectal cancers. These collective early findings promise to inform future applications of genetic and genomic advances toward tangible clinical and public health benefits.

**Overweight and obesity control.** In 1841, Quetelet first reported the concept of an index of body weight status, aptly dubbed “Quetelet’s” index until the early 1970s, when Keys and associates began the current custom of calling it body mass index (270). The first studies shedding light on how genetic testing influences the adoption of risk management behaviors (268, 269) found that notification of positive mutation carrier status can improve uptake of screening recommendations for breast and colorectal cancers. These collective early findings promise to inform future applications of genetic and genomic advances toward tangible clinical and public health benefits.

A preclinical animal study reported in 2003 provided the proof of concept that diet alters the epigenome (279), and an early preclinical study of exercise and cancer was reported in 1997 (280). This work is very important to cancer prevention because the prevalence of obesity has increased dramatically over the past 30 years, especially in children, and the study of the obesity-cancer link may lead to new preventive strategies. Recent scientific study has focused on the specific molecular basis of energy balance effects including effects on the AMP-activated protein kinase and Akt pathways (281).

**Preventing new cancers in cancer survivors.** The search phrase “cancer survivorship” prompted 235,428 entries in PubMed, beginning with a 1947 article entitled “The Factors in 5 Year Survival of Gastric Cancer: A Study of 30 Cases” (282). This work is very important to cancer prevention because the prevalence of obesity has increased dramatically over the past 30 years, especially in children, and the study of the obesity-cancer link may lead to new preventive strategies. Recent scientific study has focused on the specific molecular basis of energy balance effects including effects on the AMP-activated protein kinase and Akt pathways (281).

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1900</td>
<td>First animal prevention studies</td>
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<td>1905</td>
<td>Bacterial toxins linked to cancer treatment; preserving BCG in bladder cancer prevention (121)</td>
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<td>1910</td>
<td>Family G (158)</td>
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<td>1915</td>
<td>Observations in humans (2) confirmed by coal tar findings in rabbits (4)</td>
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<td>1920</td>
<td>2-Step chemical carcinogenesis (initiation, promotion [18])</td>
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<td>1925</td>
<td>Field carcinization</td>
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<tr>
<td>1930</td>
<td>Epidemiology leading to smoking control to prevent lung cancer (209,210)</td>
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<td>1935</td>
<td>Energy restriction studies</td>
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<td>1940</td>
<td>(273–275)</td>
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<td>1945</td>
<td>Pap test developed (189)</td>
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<td>1950</td>
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<td>First preclinical agent interventions (7)</td>
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<td>2020</td>
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**Figure 1.** Selected events that have influenced the history and progress of cancer prevention.
more effective therapies, and the increased risk of survivors not only for recurrence but second primaries as well, thus increasing the motivation of survivors to participate in behavioral research. In the early 1980s, Ganz began pioneering studies of quality-of-life assessments in cancer patients, studying cancer survivorship and late effects of cancer treatment, cancer in the elderly, and quality of care for cancer patients (285, 286). The first report of an RCT to attempt energy restriction in humans explicitly to inhibit recurrence of cancer appeared in 1993 (287). The Women’s Intervention Nutrition Study (WINS) is the first RCT of a potentially healthful diet (reduced fat intake) in humans to prevent cancer recurrence, as described in 1992 (288); interim WINS results were reported in 2006 (289). The first exercise RCT designed to prevent cancer recurrence in humans was reported in 2008 (290). The U.S. NCI established the Office of Cancer Survivorship in 1996 in recognition that many cancer patients survive for long periods of time after diagnosis and have unique and poorly understood needs.

Women’s Health Initiative

In a deviation from the norm of less detailed descriptions in this review, this section will provide greater detail on the highly complex Women’s Health Initiative (WHI) to clarify its design and outcomes, which heretofore have baffled many experts in the field, including us. With more than 161,000 women ages 50 to 79 years, the historical WHI is one of the most definitive, far-reaching research efforts ever undertaken for women’s health in the United States. WHI traces its roots back to the mid-1980s Women’s Health Trial (291), the first trial of a diet and cancer hypothesis, and the early-1990s Women’s Health Trial Feasibility Study in Minority Populations (292), both led by Henderson and Prentice. While the Minority Populations trial was under way, Healy was named the first woman director of the U.S. NIH, announcing plans during her confirmation hearings to conduct the WHI. She rolled hormone and low-fat diet trials into one program and added a calcium and vitamin D trial and an observational study, and the scope and budget of WHI were presented to and approved by Congress in the early 1990s. The RCT program randomized more than 68,100 postmenopausal women between 1993 and 1999, and the observational study of chronic disease epidemiology in women involved 93,676 women. The complex RCT (293, 294) tested three interventions to reduce the incidence of cardiovascular disease, cancer, and osteoporotic fractures. For the hormone therapy component, two parallel randomized, double-blind, placebo-controlled trials were conducted, one comparing estrogen alone with placebo (10,739 women with prior hysterectomy) and the other comparing combined estrogen plus progestin with placebo (16,608 women with an intact uterus). The primary outcome for both trials was incident coronary heart disease, with invasive breast cancer incidence as the primary safety outcome. The primary outcomes for the low-fat diet component were invasive breast and colorectal cancer, and colorectal cancer was a secondary outcome of the calcium and vitamin D trial. Regardless of the primary RCT end point(s), total and site-specific cancer incidences were documented for all WHI participants. Both WHI hormone trials were stopped early because of adverse effects. The estrogen plus progestin trial was stopped in 2002 because of adverse effects on breast cancer incidence (295, 296), leading to decreased hormone use and breast cancer rates in the general population (16,608 women with an intact uterus). The primary outcome for both trials was incident coronary heart disease, with invasive breast cancer incidence as the primary safety outcome. The primary outcomes for the low-fat diet component were invasive breast and colorectal cancer, and colorectal cancer was a secondary outcome of the calcium and vitamin D trial. Regardless of the primary RCT end point(s), total and site-specific cancer incidences were documented for all WHI participants. Both WHI hormone trials were stopped early because of adverse effects. The estrogen plus progestin trial was stopped in 2002 because of adverse effects on breast cancer incidence (295, 296), leading to decreased hormone use and breast cancer rates in the general population (297, 298), coronary heart disease (299, 300), stroke (301), and venous thromboembolisms (302). The estrogen-alone trial was stopped in 2004 because of an increased risk of stroke (303, 304). The estrogen plus progestin trial also produced a 44% [95% confidence interval (95% CI), 19–62%] reduction in risk of colorectal cancer (versus placebo; ref. 299). The low-fat diet trial

Figure 1. Continued.
produced a modest nonsignificant trend toward reduced breast cancer risk [hazard ratio (HR), 0.91; 95% CI, 0.82–1.01; ref. 305]; possibly an ovarian cancer risk reduction (306); and no reduction in colon cancer incidence (HR, 1.08; 95% CI, 0.90–1.29; ref. 307), total cancer incidence (306), or total mortality (305). The calcium and vitamin D trial had no appreciable effect on the rates of colorectal cancer (HR, 1.08; 95% CI, 0.86–1.34; ref. 308) or breast cancer (HR, 0.96; 95% CI, 0.82–1.09; ref. 309), a modest reduction in total mortality (HR, 0.91; 95% CI, 0.83–1.01; ref. 310), and no effect on total cancer incidence or mortality (308).

Conclusions

From the surgical and environmental observations and recommendations of Le Clerc and Pott in the 1700s to smoking cessation/prevention and screening/resection in the 1980s to the FDA approval of HPV vaccine for cervical cancer prevention in 2006 (to mention the barest few), the extensive history of clinical cancer prevention (Fig. 1) provides a rich backdrop against which to view and compare modern-day efforts for reducing the incidence, mortality, and burden of cancer. The past cannot exist without the future, however, and there are several exciting, promising new directions (with historical antecedents, of course) that cancer prevention will use to embroider its future history.

The recent historical trial of DFMO and sulindac in colorectal neoplasia (117) illustrates the leading future direction of molecular-targeted combinations; another promising combination in preclinical studies is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor plus an NSAID in intestinal carcinogenesis (311). The DFMO-plus-sulindac RCT opened the door to using two or more drugs for cancer prevention, echoing great earlier advances of the 1960s and early 1970s in developing combination chemotherapy for childhood leukemia and Hodgkin’s disease (312). Combinations offer the possibility to develop safer, more-effective regimens for clinical trials and practice. Their development, which deviates from the norm of clinical prevention, will require extensive preclinical support from animal studies, mechanistic in vitro studies, the clinical research community, and federal granting agencies. Barriers to combination chemoprevention development include formidable regulatory and intellectual property problems.

Vaccinations against hepatitis B–related liver cancer and HPV-related cervical cancer highlight the importance of population-wide approaches for preventing infection-related cancers (141). Major issues of this research are an increased understanding of microbial oncogenesis, identifying critical factors of the host-microbe interaction (e.g., specific agents and genotypes of microbes and hosts), and improved pharmacologic agents derived from probiotics (beneficial microbes) or prebiotics (dietary supplements as substrates to promote the growth of probiotic microbes). This is an extremely complex area of prevention, however, as illustrated by the control of H. pylori infection for gastric cancer prevention. H.
**Historical Milestones of Cancer Prevention**

**pylori eradication in the United States has not only decreased gastric cancer but also increased esophageal cancer.**

Preclinical directions include the potential of angiogenesis targeting for cancer prevention. Our historical narrative cited the seminal transgenic mouse-model research of Folkman and Hanahan in showing the angiogenic switch or shift of balance between angiogenic stimulators [e.g., vascular endothelial growth factor (VEGF)] and inhibitors, prior to invasive cancer (82–84). Later studies in clinical specimens supported the occurrence of angiogenesis during human premalignancy in the lung and other sites (313). A recent groundbreaking manifestation of this line of investigation for prevention involved findings that the angiogenesis inhibitor sunitinib (predominantly a VEGF receptor tyrosine kinase inhibitor) affected primary lung tumor development and growth, but not metastasis, in genetically engineered mice (314, 315). Surprising in light of the general belief that angiogenesis mainly mediates the processes of tumor invasion and metastasis, this recent finding supports a potentially practical approach for lung cancer prevention through angiogenesis inhibition in the lung and head and neck (315, 316). Another pathway with very exciting prevention implications is the phosphatidylinositol 3-kinase/Akt/mamalian target of rapamycin (mTOR) pathway, which is downstream of EGFR, and is activated early in lung and oral carcinogenesis (317, 318). An mTOR inhibitor can block malignant progression of preneoplastic lesions in the KRAS mouse model (319). The mTOR inhibitor rapamycin was shown to be active in preclinical oral cancer prevention (320). The promising natural agent myoinositol regressed dysplastic bronchial lesions in heavy smokers via inhibition of active Akt (71).

New imaging approaches for IEN include optical spectroscopy (e.g., light scattering spectroscopy), chromoendoscopy (321), optical coherence tomography, and in vivo molecular imaging using activatable markers (322). Recent advances in autofluorescence with probability mapping should provide a more reliable screen for detecting oral neoplasia (323). These and other promising strategies are entirely novel approaches for addressing key needs of translational and clinical prevention trials, including risk assessment, real-time/serial characterization of preneoplastic lesions, and improved response assessments. For example, it is currently impossible to assess the histopathologic or prognostic significance of colorectal polyps accurately and reliably without removing them, yet we know that the majority of such lesions are of little direct clinical consequence. This is particularly true of small polyps and flat neoplastic lesions, although a small fraction of them may harbor advanced neoplasia of clinical importance (324). In vivo assessments of such lesions could help to identify patients at greatest risk and the efficacy of chemopreventive agents against the fraction of lesions that matter most, and do so in a more accurate, reliable, and repeatable manner (325).

The deep history of preventing smoking-related cancer involves major behavioral initiatives in smoking cessation and control. Whereas policy-driven control has had the greatest impact thus far on population-wide smoking behavior, the development and testing of nicotine vaccines and nicotine control trials will come increasingly into play going forward. Another important behavioral direction is the growing study and removal of disparities in smoking behavior and health consequences among people with a lower socioeconomic status (245–249). New directions in genetic associations with smoking behavior and lung cancer development include three genome-wide association studies (326) that identified an association between single-nucleotide polymorphism variation at 15q24–15q25.1 and susceptibility to lung cancer development and possibly smoking behavior, which are major advances in this area. This chromosomal region includes two genes encoding subunits of the nicotinic acetylcholine receptor α, which is regulated by nicotine exposure. Better molecular understanding of diffuse tissue injury and drug interactions induced by cigarette smoking includes studies of diffuse gene expression and proteomic abnormalities (313, 327) and diffuse epigenetic abnormalities (328). New lung neoplasia risk modeling includes studies of methylated genes in sputum and clinical-genomic models that integrate classic demographic and other risk factors with genomic (genetic and epigenetic and germ-line and somatic) risk factors (329, 330).

The past century of cancer prevention research comprises the cutting-edge science of many Nobel laureates, members of the National Academy of Sciences, and AACR presidents going back to 1911. The efforts of these and countless other cancer prevention investigators have helped and continue to help stem the tide of cancer and save lives. Specific AACR landmarks in this effort include task forces such as the IEN Task Force (whose efforts were reported in 2002), think tanks such as the one in 2008 entitled “Charting the Future of Cancer Prevention,” working groups, the Annual AACR International Conference on Frontiers in Cancer Prevention Research (founded in 2002), and countless scientific advances reported in AACR journals including Cancer Research (founded in 1916), Cancer Epidemiology, Biomarkers & Prevention (founded in 1991), and Cancer Prevention Research (founded in 2008). Many of these innovative prevention initiatives were implemented by Foti and colleagues at AACR. We deeply hope that this Centennial series review does honor to the remarkable century of AACR contributions to cancer research. It has been a rare honor and pleasure to compile the astonishing record of cancer prevention history that we uncovered for ourselves and possibly some of you in the course of writing this review. Of course, any review owes a tremendous debt to the generally contemporaneous investigators who came before with their contributions to this or that topic under consideration. In our case in this review, however, we have enjoyed the company of many and diverse angels, both present and departed, as we discovered the rich history that makes cancer prevention such an exciting field to work in. A great joy of this project has been weaving together innumerable and disparate threads of history that, if you are like us, may seem familiar but never quite fit together before. A great pitfall, however, is that historical benchmarks and events often inspire many different points of view in the literature, not unlike varying eye-witness accounts of a crime committed in front of a large crowd. Therefore, this recitation of the historical record is based on our best estimate of the most reliable source and may differ in cases from other accounts of the same event. At least, we hope that incorporating these events into one cohesive narrative may provide a starting point for interested readers to research any specific questions they may have about exactly what happened and when.

T.S. Eliot said, “The historical sense involves a perception, not only of the pastness of the past, but of its presence…is a sense of the timeless as well as of the temporal and of the timeless and of the temporal together…is…what makes a writer most acutely conscious of his place in time, of his contemporaneity” (331). The many distant and more recent events in this history have imbued us with a sense of the eternal presence of the past.
in our own current and future research and practice of cancer prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Cancer Prevention: From 1727 to Milestones of the Past 100 Years

Scott M. Lippman and Ernest T. Hawk


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