**Historical Perspective**

**Cancer Prevention Research: Back to the Future**

Scott M. Lippman

This issue of the journal marks the first anniversary of the print editions of Cancer Prevention Research (CaPR), which seems a good time to reflect on the remarkable history of the field that CaPR is dedicated to enriching. It is fortuitous that CaPR’s first anniversary coincides with the publication of “Cancer Prevention: From 1727 to Milestones of the Past 100 Years” in Cancer Research (1), commemorating the Centennial anniversary of the American Association for Cancer Research (AACR). This Centennial paper provides a detailed narrative of the major historical advances of chemoprevention and surgical and behavioral prevention, beginning with individual-insight–derived recommendations of CG Le Clerc in 1727 (preventive surgery) and Percivall Pott in 1775 (preventive workplace measures) and culminating in the massive randomized controlled Selenium and Vitamin E [prostate] Cancer Prevention Trial (SELECT) reported in 2009.

The present historical perspective discusses the rich prevention history from which CaPR emerged and places a few important CaPR papers of the past 12 months in the context of this history. For example, CaPR articles on the investigation of new approaches to enhance cancer prevention via screening and resection of intraepithelial neoplasia (e.g., chromoendoscopy and autofluorescence probability mapping; refs. 2, 3) are rooted in the 1829 observations of Récamier on the tendency of preexisting benign lesions to become cancerous; the work of Papanicolaou and others from 1928 through the 1950s (13) fundamentally support the entire concept of chemoprevention conceptismultistep carcinogenesis, which evolved from the classic two-step chemical carcinogenesis model first reported in 1938 (10) to the elegant 1954 studies of Auerbach providing some of the first detailed histologic data on multistep progression (from hyperplasia to metaplasia to dysplasia to carcinoma in situ to cancer) in the lung; he noted the direct relationship of this progression with intensity of smoking in 1957 (11, 12). In 1988, Vogelstein provided the first characterization of molecular progression within multistep carcinogenesis (13), detailing it in the colon–rectum. Molecular progression models were soon described by Sidransky and others for several sites of neoplasia (14). The field concept justifies systemic versus local control of diffuse, frequently invisible preinvasive conditions, and the multistep concept justifies chemopreventive interventions to arrest, reverse, or eradicate specific steps of neoplasia before it progresses to invasion.

Wattenberg invented the term “chemoprophylaxis” in a landmark 1966 review of cancer prevention studies in chemically induced animal carcinogenesis models (15). He surveyed prevention-related animal studies ranging from a 1929 study of mustard gas in inhibiting tar-induced skin carcinogenesis (16) to the early mechanistic studies of Lacassagne (17), Conney (18), Huggins (19), and his own in the 1950s and 1960s (20–22). Talalay helped extend this work in the late 1970s with mechanistic preclinical studies of preventive natural antioxidants, labeling these studies “chemoprotection” (23).

In 1967, Bollag began the first syntheses of analogues of vitamin A (24), thus building on the vitamin A research of Wollbach and Howe (4) and a few subsequent investigators (25, 26). It was hoped that these vitamin A analogues would be as or more effective than would be vitamin A itself but with reduced toxicity (hypervitaminosis A), which was reported as early as 1597 by European Arctic explorers, who developed severe symptoms after eating polar bear liver (27, 28). Sporn

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**Chemoprevention**

A 1925 report of Wollbach and Howe on the acquisition of neoplastic properties by epithelial tissues following the deprivation of fat-soluble vitamin A and “the reverse changes that follow in the rapid amelioration when the rats are restored to an adequate diet” (4) possibly is the first report of a preclinical chemoprevention study. Two biological concepts proposed in the 1950s fundamentally support the entire concept of chemoprevention. First, Slaughter and colleagues described “field cancerization” in 1953 (5), basing this concept on findings in histologically abnormal tissue surrounding oral cancer. They postulated that insulin from a carcinoma occurs across the entire epithelial field, giving rise to multiple, independent sites of carcinogenesis, a concept that was extended to other aerodigestive tract sites in 1984 (6) and ultimately to virtually every epithelial site. Early molecular elucidations of field effects include the intraepithelial spread of genetically related oral premalignant clones (7) and clonal patches (characterized by clonal expansion and diversity; refs. 8, 9). The second critical chemoprevention concept is multistep carcinogenesis, which evolved from the classic two-step chemical carcinogenesis model first reported in 1938 (10) to the elegant 1954 studies of Auerbach providing some of the first detailed histologic data on multistep progression (from hyperplasia to metaplasia to dysplasia to carcinoma in situ to cancer) in the lung; he noted the direct relationship of this progression with intensity of smoking in 1957 (11, 12). In 1988, Vogelstein provided the first characterization of molecular progression within multistep carcinogenesis (13), detailing it in the colon–rectum. Molecular progression models were soon described by Sidransky and others for several sites of neoplasia (14). The field concept justifies systemic versus local control of diffuse, frequently invisible preinvasive conditions, and the multistep concept justifies chemopreventive interventions to arrest, reverse, or eradicate specific steps of neoplasia before it progresses to invasion.

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introduced the modern terms “retinoids” for vitamin A analogues and “chemoprevention” for the development of cancer-preventive agents in 1976 (29).

Early preclinical molecular-targeted research included that by Lacassagne in 1932-1933 presaging molecular-targeted prevention of breast cancer. He reported that estrogen could induce mammary tumors in mice and introduced the concept that estrogen antagonism could prevent breast cancer (30–32). Following the 1966 discovery of the estrogen receptor (33), Jordan showed that the selective estrogen receptor modulator tamoxifen prevented mammary tumors in rats in 1974 (34). Huggins received a 1966 Nobel Prize for work related to preventive and therapeutic molecular targeting in the prostate beginning with his 1941 report that castration had a beneficial effect on metastatic prostate cancer (35). Presaging clinical cyclooxygenase (COX)-2 targeting for hereditary and sporadic colorectal cancer prevention, reports by DuBois and colleagues in 1994 and Taketo and colleagues in 1996 showed that COX-2 is up-regulated in human colorectal adenomas and adenocarcinomas (36) and could be targeted effectively for controlling intestinal neoplasia in adenomatous polyposis coli (Apc)-knockout mice (37).

In 1989 and 1996, Folkman, Hanahan, and colleagues contributed seminal reports on the “angiogenic switch” (38, 39), following in 1999 with a report of the chemopreventive effects of antiangiogenic agents in mice (40). CaPR published possibly the first study of angiogenesis targeting in genetically engineered mouse lung carcinogenesis (41), assessing sunitinib (thought to primarily affect the vascular endothelial growth factor receptor [VEGFR]), and published a study of CD36 targeting in chemically induced oral carcinogenesis (42). Four other CaPR papers report targeting in the angiogenesis-related phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway (43)—AKT inhibition with the natural agent myoinositol in human bronchial dysplasia (44), which built on earlier work by this group and others in targeting mTOR in genetically engineered mouse lungs (45, 46); mTOR inhibition for preventing chemically induced mouse oral carcinogenesis (47); and in vitro and animal model targeting in this pathway with analogues of the natural agent deguelin (48, 49). As highlighted by these papers and a CaPR perspective article (50), targeting angiogenesis and the microenvironment are an exciting new frontier of cancer chemoprevention.

Early clinical cancer prevention centered largely on trials of diet- and nutrition-related agents and compounds. Pilot clinical trials by Stich and Rosin of the late 1970s and early 1980s tested retinoids in betel nut chewers of India, Philippines, Taiwan, Guam, and Russia and other patients with the premalignant condition oral leukoplasia (51). Beginning in 1982, Alberts, Meyskens, and colleagues reported phase I and II trials of a topical retinoid for cervical dysplasia, leading to a phase III randomized controlled trial (RCT) reported in 1994 (52) that produced significant activity in moderate but not severe cervical dysplasia. The pioneering translational research program of Hong and colleagues began in 1982 with an RCT showing the significant activity of a high-dose of the retinoid 13-cis-retinoic acid (13cRA) against oral leukoplasia (53). This group began a proof-of-principle RCT in 1983, showing that adjuvant high-dose 13cRA prevented secondary primary tumors in patients with curatively treated head and neck cancer (54). This regimen was too toxic and reversible for cancer prevention, and lower, more tolerable doses did not translate into long-term cancer risk reduction (55, 56). These researchers pioneered modern translational methods by integrating correlative and other adjunctive analyses of retinoic acid receptors, p53, loss of heterozygosity, cyclin D1, and other biomarkers within their clinical trials (57–61). For example, a major trial of this group (62) provided patients for the translational finding of Lotan and colleagues that retinoic acid receptor-β expression was suppressed in oral leukoplasia and could be up-regulated by 13cRA (63), thus helping to translate the 1987 codiscovery of the first nuclear retinoic acid receptor by Chambon (64) and Evans (65). Another important nutrient trial with a noncancer end point involved calcium and was conducted in the 1990s; this trial reduced adenoma risk by 19% (66).

Launched in 1985, the earliest cancer end point (definitive) RCTs involved nutritional supplements. The definitive prevention RCTs have been largely negative-neutral, with harm being the exception to neutral results (67). As reported in 1994 and 1996, the Alpha-Tocopherol and Beta-Carotene (ATBC) trial (68) and Beta-Carotene and Retinol Efficacy Trial (CARET; ref. 69) found a stunning harmful effect of β-carotene in increasing the risk of lung cancer in high-risk smokers. A high-profile 1981 epidemiology review article by Peto and colleagues (70) has been frequently cited as a key factor leading to the design and implementation of these and other β-carotene RCTs (71, 72). Adjuvant lung and head-and-neck RCTs of low-dose 13cRA produced overall negative-neutral results in 2001 (56) and 2006 (55). The long series of definitive large-scale nutrient trials was capped recently by the negative-neutral SELECT (73, 74), which arose, in part, from suggestive secondary RCT findings of 1993 (75), 1994 (68) and 1996 (76). After the disappointing 2009 findings of SELECT, many experts in the field believed that “the prospects for cancer prevention through micronutrient supplementation have never looked worse” (77).

The strong support of epidemiologic cohort studies for micronutrients in cancer prevention did not pan out in the RCTs, which hypothesized that specific nutrients could be extracted from the epidemiologic associations based on more complex dietary patterns. The negative RCT results suggest that this reductive approach oversimplified the epidemiologic associations. Several factors including relative macronutrient density, complex mixtures of bioactive compounds, nutrient deficiency, and nutrigenetic factors (74, 77–79) are now postulated as important to any potential benefit of foods in reducing cancer risk. Dietary interventions addressing these issues are discussed below in Behavioral Prevention.

The negative course of definitive RCTs shifted in 1998 with the report of the first molecular-targeted prevention RCT, the landmark Breast Cancer Prevention Trial (BCPT), which also was the first clinical trial of an agent for reducing breast cancer risk. The selective estrogen receptor modulator tamoxifen reduced breast cancer risk by 50% in BCPT (80), which was designed and implemented largely on the basis of 1980s and subsequent studies of positive adjuvant trials of tamoxifen in reducing the risk of contralateral breast cancer (81); the concept of tamoxifen for primary breast cancer prevention was introduced in 1991 (82). Subsequent positive results with molecular-targeted agents included those reported in 2000 for the COX-2-specific inhibitor celecoxib in familial adenomatous polyposis patients (83) and results reported for the
selective estrogen receptor modulator raloxifene in the Study of Tamoxifen and Raloxifene (STAR; ref. 84). All three agents have received Food and Drug Administration (FDA) chemopreventive approvals. A long-term follow-up study of tamoxifen showed that benefits persisted for and toxic effects were off within 10 years (or 5 years after tamoxifen treatment stopped; ref. 85). These trials helped realize the historical promise of estrogen and estrogen receptor research beginning in 1932-1933 (31–34) and COX-2 discoveries of the 1990s (36, 37). Key figures in the development and implementation of the breast prevention RCTs were Ford of the National Cancer Institute and Fisher.

Molecular-targeted cancer prevention advanced further in 2003 with the large-scale Prostate Cancer Prevention Trial (PCPT) of the 5α-reductase inhibitor finasteride (86). Finasteride significantly reduced prostate cancer risk but also apparently increased high-grade prostate cancer and only prevented clinically insignificant disease. PCPT built on the 1941 work of Huggins involving hormone modulation effects on metastatic prostate cancer (35). The apparent toxicity involving high-grade disease stymied the acceptance of finasteride for prostate cancer prevention despite its statistically significant cancer-preventive effects. New PCPT analyses reported in CaPR, however, have renewed hope for hormonal prostate cancer prevention with finasteride. These analyses found that finasteride prevented clinically meaningful disease and did not increase aggressive disease (87-90), possibly eventually eliminating the related obstacles to finasteride acceptance (86). The case for this agent class has been further strengthened by very recently reported results of a trial of another 5α-reductase inhibitor, dutasteride. In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial (91), dutasteride reduced prostate cancer risk by 23% and did not statistically significantly increase high-grade prostate cancer in a higher-risk group (e.g., elevated prostate-specific antigen) than that of PCPT. These results have important regulatory implications for prostate cancer prevention.

Reported in 1993, the first RCT to show substantial chemopreventive effects in the setting of colorectal adenomas involved the nonsteroidal anti-inflammatory drug (NSAID) sulindac (92). RCTs of aspirin also have significantly reduced the risk of adenomas (93), and pooled analyses of cardiovascular-protection RCTs indicate that aspirin significantly reduces the risk of colorectal cancer (94). High-dose aspirin prevented colorectal cancer that expresses COX-2 (95), consistent with results of three important RCTs of COX-2-selective inhibitors: the Adenomatous Polypl Prevention on Vioxx (APPROVe), Adenoma Prevention with Celecoxib (APC), and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials, all stopped early (and before published efficacy results) because of interim analyses in APPROVe and APC showing unexpected increases in cardiovascular event rates (96–98). The significant colorectal adenoma reductions in each of these trials were reported in 2006 (96, 99, 100). In 2008, a pooled analysis found that people with a low baseline cardiovascular risk seemed to have no increased risk of serious cardiovascular events in major celecoxib RCTs (101).

Several CaPR papers extend this area of research, including studies of the biology of adverse cardiovascular events and other (than COX-2) targets within this pathway (102–110). The final planned analysis of the APC trial found that a history of atherosclerotic heart disease was the only specific risk factor that interacted significantly with celecoxib in producing adverse cardiovascular events (102), extending less specific earlier suggestions (101) and moving toward realizing the promise of historical molecular studies of COX-2 inhibition (36, 37). The only randomized clinical trial data on cardiovascular risk associated with a non–COX-2–specific NSAID showed a risk that was consistent with that of specific COX-2–inhibiting NSAIDs (107). Another CaPR report detailed the relationship between aberrant crypt foci and cancer outcome in the APC trial, finding no correlation between the precursor and cancer end point in the largest prospective evaluation of aberrant crypt foci and the only such evaluation in a trial of an active agent (108). The DuBois and Markowitz groups discovered the importance of the termination of the COX-2 product prostaglandin E2 by 15-hydroxyprostaglandin dehydrogenase (109) in colorectal carcinogenesis. Prostaglandin E2 was known to have a very short half-life in blood because of inactivation in the lung, but where 15-hydroxyprostaglandin dehydrogenase operated in the lung remained unknown. A CaPR article of the Dannenberg group first reported that 15-hydroxyprostaglandin dehydrogenase localizes in pulmonary microcytes of normal lung tissue and is lost in lung tumor tissue (106). A CaPR paper from the DuBois group (110) reported the novel discovery that prostaglandin transport is extremely important to prostaglandin metabolism and potential NSAID effects in the colon-rectum, suggesting a new realm of targets for colorectal cancer chemoprevention.

Sporn proposed the development of combinations to overcome limitations (e.g., lesser efficacy) of single agents for chemoprevention in 1980 (111). CaPR published a recent landmark trial of the combination difluoromethylornithine (targeting ornithine decarboxylase) and sulindac (targeting COXs), which reduced overall colorectal adenoma recurrence by 70% and advanced and/or multiple adenomas by more than 90% (112). This trial built directly on a 1986 preclinical study of difluoromethylornithine plus an NSAID (113) and provided the first clinical validation of Sporn’s proposal. Preclinical and clinical combinations will be a major focus of future CaPR articles.

There are several notable historical areas of chemoprevention besides micronutrients and molecular-targeted drugs. In 1984, Taiwan implemented a national program to vaccinate children against a major risk factor for liver cancer, hepatitis B (114), substantially lowering liver cancer risk. The hepatitis B vaccine had been developed in 1976, the same year that Blumberg was awarded the Nobel Prize for his 1967 discovery of the hepatitis B virus (115) and 1975 discovery of its link with liver cancer (116). Important historical roots also attach to the landmark development of human papillomavirus (HPV) vaccine for preventing cervical cancer. The HPV-cervical cancer link was reported in 1974 by zur Hausen (117, 118), who also discovered in 1983 the first specific HPV (type 16) in cervical cancer patients (119). The 1983 discovery led to an RCT of HPV-16 vaccine (120) that proved the principle established later by RCTs begun in 1991 that tested quadrivalent and bivalent HPV vaccines to prevent cervical neoplasia in girls and young women (121); the FDA inapproved quadrivalent HPV vaccination for preventing cervical cancer; cervical adenocarcinoma in situ; and high-grade cervical, vulvar, and vaginal intraepithelial neoplasia in 2006. zur Hausen received a 2008 Nobel Prize for his work
in this area, and HPV was recently linked to oropharyngeal cancer development (122).

In 1989 and 1991, the Blaser group and others (123–125) established an association between Helicobacter (H.) pylori and gastric cancer and premalignant gastric lesions, and H. pylori is now recognized as the major worldwide cause of stomach cancer. This setting, however, illustrates the complexity of controlling infection-related cancers because eradicating H. pylori not only decreases stomach cancer but also may increase esophageal adenocarcinoma, which has the fastest-increasing cancer incidence in many Western countries. The inverse association between H. pylori and gastroesophageal junction adenocarcinoma was reported in 1997 (126). The harmful effect of H. pylori involves noncardiac gastric cancer, and the protective effect involves esophageal and cardia gastric cancers (127). The risk of gastric cancer and the protective effect against esophageal cancer were most strongly associated with cagA+ strains of H. pylori discovered in 1989 (128, 129). A recent RCT of H. pylori eradication reduced the occurrence of metachronous gastric cancer in patients resected for early gastric cancer (130). A Nobel Prize for discovering H. pylori and linking it with duodenal and gastric diseases was awarded to Marshall and Warren in 2005 (131).

The roots of modern intravesical bacillus Calmette-Guérin (BCG) for preventing recurrence of superficial (noninvasive) bladder tumors lie in the 1893 observation of Coley that cancer patients can respond to toxic bacterial products (132). Other important dates in the cancer chemoprevention development of BCG are 1908, when BCG was developed as a tuberculous vaccine in France; 1921, when it was first used against tuberculosis in humans; 1935, when it was first used (in Sweden) as a cancer vaccine; the late 1950s to 1960s, when experimental and clinical studies generated enthusiasm for BCG in various cancers (133); 1976, when Moraes et al. reported the first study of the effects of intravesical BCG on superficial bladder cancer (for which radical cystectomy was standard at this time; refs. 134, 135); and 1990, when the FDA approved BCG for preventing recurrence of superficial bladder cancer based on clinical trials by the Southwest Oncology Group (136) and other investigators.

Oral contraceptive pills have reduced the risks of ovarian (137) and endometrial (138, 139) cancers in multicenter, population-based, case-control studies of 1983 and 1987 (by about 40%) and reduced ovarian cancer risk in BRCA1 and BRCA2 mutation carriers (from 40% to 60%; refs. 140, 141). Oral contraceptive pills are accepted as effective risk-reducing agents and are recommended as such under certain circumstances for hereditary high-risk women (142, 143).

### Surgical Prevention

The two major areas of cancer-preventive surgery are screening-associated removal of premalignant lesions and prophylactic surgery. Récamier anticipated both areas in his 1829 comments that “constitutional” cancers can be hereditary and the cause of acquired or spontaneous cancers can be due to degeneration of preexisting benign lesions (144). In the 1920s, Papanicolaou began studies of aberrant cytology in cervical, vaginal, and endometrial cells sampled in the vagina, leading to his namesake Pap test, which was validated as a diagnostic tool in 1943 (145) and refined several times, for example, in the 1988 National Cancer Institute–sponsored Bethesda System (146). Pap screening primarily detects cervical neoplasia and serves to reduce the incidence and mortality of cervical cancer (147–149). HPV screening is becoming increasingly important as an adjunct to the Pap test and as an independent factor in cervical neoplasia screening (150).

Leborgne classified breast microcancer in 1950 (151, 152), and the first mammography-specific X-ray equipment was introduced in 1956. Widespread screening mammography dramatically increased the detection of DCIS by the early 1980s, when cancer-preventive DCIS treatment included incision with or without radiation and unilateral or bilateral mastectomy. Although still common for DCIS, mastectomy had become questionable and lumpectomy more common for invasive disease by 1985 (153). Fisher and colleagues compared the less morbid DCIS treatment options with each other (154) in a trial begun in 1985. They found that lumpectomy plus radiotherapy prevented invasive cancer better than did lumpectomy alone in DCIS patients and subsequently found that lumpectomy plus radiation plus tamoxifen was more effective than was lumpectomy plus radiation (154). Begun in 1980, the observational National Polyp Study (155) of colonoscopic screening and polypectomy, a practice begun in the 1960s (156), reported in 1993 that regular surveillance and polypectomy for adenomas resulted in up to a 90% reduced colorectal cancer incidence (compared with three historical control groups). As reported in CaPR, major efforts are under way to increase the sensitivity, specificity, and efficacy of screening-guided treatments for cancer prevention. Two of these papers explored chromoendoscopy screening for polypectomy (3, 157), and another explored an algorithm for the objective, reproducible interpretation of autofluorescence screening for neoplasia in the oral cavity (2, 158, 159).

The other major cancer-preventive surgical approach is prophylactic surgery in high-risk people with heritable (germline) genetic disorders. A preclinical study reported in 1916 by Lathrop and Loeb examined cancer prevention through castration (oophorectomy) in female mice (160). This is possibly the first preclinical cancer prevention paper, published 140 years after the observational and interventional contributions of Percivall Pott in humans (161). In 1895, Aldred Scott Warthin foreshadowed prophylactic, organ-removing surgery for preventing hereditary cancers with his early observations of an unusually high intergenerational prevalence of cancer in “family G” (162). Maud Slye echoed Warthin’s human observations in a 1916 paper on “inheritable” cancers in mice (163), contemporaneous in year and journal with the 1916 Lathrop and Loeb article discussed above (160). Reported as early as 1901, prophylactic colectomy in patients with “familial polyposis of the colon” became standard colorectal cancer prevention by no later than 1948 (164, 165). The cancer history of family G was updated most recently by Lynch in 1971 (166), and he first recommended prophylactic, organ-removing surgery in people at risk of heritable cancers in 1977 (167). A high familial prevalence of colon and endometrial cancer was originally called the Cancer Family Syndrome and now is called hereditary nonpolyposis colorectal cancer syndrome, or Lynch syndrome. Lynch made several historical recommendations, including the following examples: total colectomy, rather than hemicolectomy, for initial colorectal cancer in an extremely high-risk relative, for Cancer Research.
sized ability of prophylactic surgery to reduce hereditary disease and interventions. Molecular papers dating from 1987 and provide opportunities for testing tailored cancer surveillance and interventions. Molecular papers dating from 1987 validated the clinical observations of Lynch and his predecessors (176–180) on hereditary cancer syndromes by identifying the relevant germ-line changes (178, 180–184). Recent large observational cohort studies confirmed the hypothesized ability of prophylactic surgery to reduce hereditary cancer risk (142, 185–188).

**Behavioral Prevention**

As highlighted by Doll and Peto in a landmark epidemiology review of 1981 (189), many causes of cancer could be avoided through changes in behavior related to smoking, diet, and other factors. The strong link between cancer prevention and cancer epidemiology is exemplified by the epidemiology of smoking-related lung cancer risk including observations dating back to the 1700s (190). The history of smoking various materials dates to at least the 5th century B.C.E. (191). Smoking tobacco, a plant native to the Americas, however, began among native Americans well before Europeans adopted the custom following Columbus’ discovery of Cuba and Hispaniola in 1492. By 1940, cigarette smoking reached a U.S. prevalence of 65% among men born between 1911 and 1920, stayed at about this level until 1955, and has declined steadily, in general, since then. Smoking began to increase among U.S. women in the 1930s, peaked at 38% in 1960, and has declined since then, although less so than among men (192). Wynder and Doll fully demonstrated the long-suspected association between cigarette smoking and lung cancer risk in seminal epidemiologic studies of 1950 (193, 194), and this association was established by the U.S. Surgeon General’s Report of 1964, which added the data of Auerbach on smoking-related neoplasia in lung tissue to the compelling epidemiologic evidence. This report prompted major public policy measures with an immediate impact on cigarette smoking. By 1965, the overall U.S. cigarette smoking rate was down to 41.9%. Impactful smoking-control regulations, including nonsmoking public areas and the smoke-free workplace, emerged in the 1970s, and the overall age-adjusted U.S. smoking rate decreased to 33.3% by 1979.1

The addictive nature of tobacco use became a topic of scientific literature in the early 1900s (195). The biology of carcinogenesis induced by the numerous carcinogens in tobacco smoke began to be reported at least as early as the 1950s (196–198). Multifaceted research of the 1970s focused on nicotine, the addictive component of tobacco (or Nicotiana; refs. 195, 199). Work by molecular epidemiology pioneer Spitz and colleagues and others in dopamine receptor genes (200) reflects an important advance in understanding genetic influences on tobacco dependence. In the 1970s, Peto predicted one billion avoidable deaths in the 20th century if then-current smoking patterns persisted and (with Doll) showed that half of all persistent smokers would eventually die of smoking, a risk that lessened with smoking cessation. There are three classes of FDA-approved smoking-control agents: nicotine replacement [e.g., in gum (the first such therapy, which was approved in 1984) and patches (199, 201)]; bupropion antidepressant products; and varenicline, a nicotinic acetylcholine partial agonist (202). The impact of behavioral trials of smoking cessation [e.g., the Community Intervention Trial for Smoking Cessation (COMMIT), launched in 1988; refs. 203, 204] has been less than that of public policy measures, reflected by the American Stop Smoking Intervention Study (ASSIST; implemented from 1993 through 1999; ref. 205). The first pharmacogenetic studies of tobacco dependence treatment, including assessments of dopamine-pathway polymorphisms (206, 207), were reported in 2002-2003 by Lerman and others. Many experts believe, however, that the impact of clinical trials will grow with better targeting of the most appropriate smoking populations. The overall age-adjusted U.S. smoking rate in people 18 years and older was 24.8% in 1995.1

Grizt advanced our understanding of cigarette smoking behavior in women and other special populations through research contributions to the 1980 U.S. Surgeon General’s report entitled “The Health Consequences of Smoking for Women” (208). The detection of important disparities in smoking behavior and health consequences among people with a lower versus a higher socioeconomic status began in the mid-1990s (209–213), and initiatives to eliminate barriers and increase access to smoking cessation and control programs

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among low socioeconomic status groups (214–218) were recommended in “Making Cancer Health Disparities History: Report of the Trans-HSS Cancer Health Disparities Progress Review Group, 2004.” Total U.S. cancer deaths declined in the late 1990s, driven largely by a reduction in male lung cancer after 30 years of declining smoking rates (219). The overall age-adjusted U.S. smoking rate in people 18 years and older dropped to 20.8% in 2006, which is half the 41.9% rate of 1965.

Important tobacco biology studies such as one in 1978 identifying tobacco-specific nitrosamines in animal models (220) broke ground for CaPR papers on fieldwide tissue injury involving complex genomic and epigenetic alterations including in vitro (221) and clinical specimen (222) gene expression studies that extended and confirmed important 1994 findings in smokers’ lung tissues (223). Preclinical and clinical articles on proteomic, epigenomic, and genomic studies of tobacco-induced and other carcinogenesis are a major focus of upcoming CaPR articles (224). This work contributes to identifying potential new drug targets and molecular factors to be integrated into cancer risk models and to improving the understanding of adverse drug interactions (106, 225–230).

Other important realms of behavioral science are psychosocial research in the area of genetic testing for cancer risk, overweight and obesity control, and cancer survivorship. In 1982, Kessler first defined a psychological model for general genetic counseling (231), a model that was relevant to the needs of individuals undergoing cancer-related genetic counseling. Several important studies published in 1992-1993 established the increased psychological distress of women who had closer relatives with breast cancer (232–234). This research gave rise to important concerns when clinical genetic testing for hereditary cancer risk subsequently became available despite its adverse psychological consequences. Lerman and others reported the first two studies of how people respond to results of testing (for BRCA1/BRCA2 in this case) in 1996-1997 (235, 236); no personal history of cancer and a positive test increased the risk of psychological distress, and a negative test was associated with a psychological benefit. Other notable advances in understanding the behavioral aspects of genetic testing include the importance of informed consent (237) and of addressing both educational and psychosocial needs (238) and the improved uptake of screening recommendations for breast and colorectal cancers after notification of positive mutation carrier status (239, 240).

Quetelet introduced “Quetelet’s” index in 1841 in reference to body weight status, and Keys and associates initiated the current term, body mass index, in the early 1970s (241, 242). Studies of the effect of energy restriction on transplanted, chemically induced, and spontaneous tumors in mice began to appear in 1909 (243), followed in the 1940s by seminal studies of Tannenbaum and others of energy restriction and the activity and energy restriction on mammary carcinogenesis (244, 245); in 1956 by the first study of energy restriction in humans (246); and in the early 1990s by the first RCTs of altered diets (e.g., low fat) explicitly designed to reduce the risk of primary cancer or cancer precursors in humans, which were the Women's Health Initiative (WHI) trial (247–249) for reducing primary breast and colorectal cancer and the Polyp Prevention Trial (250), which did not lower adenoma risk. A recent WHI finding involving proliferative breast disease was reported in CaPR (249).

The concept of diet-gene interactions was first posited in 1969 (251). A proof-of-principle animal study showing that diet alters the epigenome was reported in 2003 (252). The rapidly increasing prevalence of obesity over the past 30 years, especially in children, and the growing understanding of its link to cancer consequences underscore the increasing importance of this area of cancer prevention. CaPR papers in this area of research include a study of the effects of physical activity and energy restriction on mammary carcinogenesis (253), extending work on this topic by other strong groups, and a related study showing dietary energy balance effects on cell signaling pathways, notably adenosine monophosphate (AMP)-activated protein kinase and Akt/mTOR, within multiple epithelial tissues in mice (254). Other preclinical CaPR papers have reported evaluations of global gene expression patterns associated with high-fat and low-fat diets (255).

Study of cancer survivorship began at least as early as 1947 (256), and promoting healthy behaviors among cancer survivors is an increasingly important area of behavioral science research (257, 258). Behavioral interventions in cancer survivors are designed to prevent recurrence and are enhanced by improvements in early detection, more effective therapies, and survivors’ high risks of recurrence and second primaries. Pioneering studies of the early 1980s by Ganz increased the understanding of quality of life in cancer patients, later effects of cancer treatment, cancer in the elderly, and quality of cancer patient care (259, 260). Specific firsts in clinical/behavioral RCTs in cancer survivors to prevent recurrence include an RCT of energy restriction reported in 1993 (261); the Women's Intervention Nutrition Study (WINS) of a potentially healthful diet (reduced fat intake) described in 1992 (262) and reported for interim results in 2006 (263); and an RCT of exercise reported in 2008 (264).

Conclusions

As with all sojourns, this visit to the exciting past of cancer prevention and journey back to the future of this past, as written in important part, I believe, within the pages of CaPR, must end. If putting CaPR in the historical context outlined here gives the appearance of unseemly self-congratulation—guilty as charged. On this occasion of the first anniversary issue of CaPR, I congratulate myself on being the luckiest editor-in-chief alive in having the support, resources, and expertise of the AACR; the extraordinary CaPR Deputy and Senior editors and Editorial Board members; and of the profound pool of prevention experts who have graced or will grace the pages of CaPR with their exciting contributions of research and thought to the future history of cancer prevention. Writing in 1919 about worthwhile literature, T.S. Eliot said that “great labor” is needed to acquire an “historical sense” (265), which is indispensable to liberating contemporary work from trendy but ultimately baseless recent directions and linking it with universal values transcending the generations. By the great labor of its editors and contributors, CaPR strives to publish lasting work that builds on the remarkable past and promises to become recognized by future historians of cancer prevention. One year down, a long, bright future to go.

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