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JNCI and Cancer Prevention

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Abstract

The *Journal of the National Cancer Institute* (*JNCI*), with its broad coverage of bench research, epidemiologic studies, and clinical trials, has a long history of publishing practice-changing studies in cancer prevention and public health. These include studies of tobacco cessation, chemoprevention, and nutrition. The landmark Breast Cancer Prevention Trial (BCPT)—the first large trial to prove efficacy of a preventive medication for a major malignancy—was published in the Journal, as were key ancillary papers to the BCPT. Even when *JNCI* was not the publication venue for the main trial outcomes, conceptual and design discussions leading to the trial as well as critical follow-up analyses based on trial data from the Prostate Cancer Prevention Trial (PCPT) and the Selenium and Vitamin E Chemoprevention Trial (SELECT) were published in the Journal. The Journal has also published important evidence on very charged topics, such as the purported link between abortion and breast cancer risk. In summary, *JNCI* has been at the forefront of numerous major publications related to cancer prevention.

Introduction

Cancer prevention research, based on a thorough understanding of trends in cancer incidence and mortality (1), has been well represented through the years in publications in the *Journal of the National Cancer Institute* (*JNCI*). In particular, major large prospective randomized controlled trials of tobacco cessation and chemopreventive and nutritional preventive approaches have influenced clinical practice and ultimately public health. Even when it was not the publication venue for the main trial outcomes, conceptual and design discussions as well as critical follow-up analyses based on trial data are often presented in the Journal.

Risk Factors and Risk Assessment

JNCI has a long history of publishing epidemiologic research exploring associations of putative risk factors with various cancers (2). As an example, exposure to diesel fumes in certain railway occupations is associated with increased lung cancer risk (3). Based on data generated as far back as the 1970s

through the 1990s (2–4), the 9th Report on Carcinogens (2000) prepared by the National Toxicology Program (National Institute of Environmental Health Sciences, National Institutes of Health) classified diesel exhaust particulates as "reasonably anticipated to be a human carcinogen" (http://www.nih.gov/news/pr/may2000/niehs-15.htm). These observations provided a foundation for the US Environmental Protection Agency's (EPA) Health Assessment Document for Diesel Engine Exhaust (Final 2002), stating that "long-term (i.e., chronic) inhalation exposure is likely to pose a lung cancer hazard to humans, as well as damage the lung in other ways depending on exposure" (http://www.cancer.gov/newscenter/newsfromnci/2012/DieselMinersQandA). More recently the Diesel Exhaust in Miners Study (DEMS), which involved 12 315 workers in eight nonmetal mining facilities, led to findings that supported an association of diesel exhaust with lung cancer, as reported in the Journal. A case-control study nested within the DEMS showed that occupational exposure to diesel exhaust may increase the risk of lung cancer (5). An additional assessment of this cohort showed that lung cancer

mortality varied by extent of exposure, ever-underground vs surface-only exposure (6–7). In June 2012, the World Health Organization's International Agency for Research on Cancer (IARC) declared diesel exhaust to be a known human carcinogen (http://www.msha.gov/Alerts/012013DPMAlert.pdf).

A particularly controversial area discussed in the Journal involves cell phones, which emit nonionizing radiofrequency waves at lower energy than is required to directly damage DNA. The phones came into common use in Scandinavia in the 1980s and in the United States in the1990s. Studies on the potential health consequences of this new technology, used by over 90% of the population, were initially triggered by anecdotal reports of brain tumors in cell phone users (8–9). Given the proximity of cell phones to the head, attention has been directed primarily to brain tumors (8), but also other tumors of the head and neck (10). In a large cohort study of persons in Denmark who began use of mobile phones between 1982 and 1995 (10–11), no association was observed between risk of cancer and cell phone use. This reinforced results of a time trend analysis of brain tumors (gliomas, meningiomas) in Scandinavia showing no change in incidence trends from 1974 to 2003. A case-control study in Scandinavia and Switzerland also revealed no association between cell phone exposure and brain tumor risk in children (12). An insightful *JNCI* editorial by Boice and Tarone reviewed the nature of the persistent controversy (9).

Breast cancer risk is generally believed to be elevated with increased exposure to circulating endogenous and exogenous estrogens, an area covered extensively in the Journal (13–14). A 1990 Special Report in *JNCI* commemorating the 30th anniversary of "the pill" (15) brought attention to the complexity of the question of whether oral contraceptive pills (OCPs) have protective, deleterious, or no effects on breast cancer risk, noting that the association may vary with age, duration of exposure, current vs past use, and other factors. Two papers concluded that overall past use of OCPs is not consistently associated with breast cancer risk (16–17). In contrast, current use of combined (low, medium, and high estrogen doses) OCPs (18) and use of OCPs for six or more months by women younger than 45 years (19) appear to be associated with elevated risk. In the aggregate, these outcomes suggest little, if any, adverse effect on risk.

Nor has the Journal shied away from other controversial but important issues, as in claims that induced abortion raises the risk of breast cancer. *JNCI* has published studies showing both positive (20–21) and negative (14) links between induced abortion and breast cancer (14,20-21). In addition, editorials examining this topic have focused on factors that could feed into this inconsistency. Important confounding factors and biases inherent in some study designs have been explored in this context (22–23).

Validated risk models play an important role in cancer prevention and screening. The "Gail model" is a prototypic example. In the United States this statistical risk model serves as the basis for assessing breast cancer risk for clinical trial eligibility and for routine clinical assessment of individual risk (National Cancer Institute's Breast Cancer Risk Assessment Tool [BCRAT], available online at http://www.cancer.gov/bcrisktool). The Gail model incorporates a number of estrogen-related (age at menarche, age at first live birth) and other risk factors, including number of previous breast biopsies, and number of first-degree relatives with breast cancer. It is used extensively in counseling women about preventive interventions. The original 1989 risk model (24) has been validated using data from several large studies: the Nurses' Health Study (25), the Breast Cancer Prevention Trial (see below) (26), and the Florence-European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort (27). It has undergone several modifications to allow greater applicability to specific ethnic groups, African Americans (28) and Asians/pacific islanders (29). In addition, the impact of incorporating data from evolving risk assessment technologies into the model has been investigated. Seven high-risk single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWASs) have minimal influence on the discriminatory accuracy of the model (30). Similarly, inclusion of mammographic density (31–32) conferred small improvements in discriminatory accuracy over the earlier model (33). *JNCI* publications have also served as a forum for comparison of the original Gail model to alternative breast cancer risk assessment tools (34–36), providing possible refinements in risk counseling.

Prevention Trials Using Chemopreventive Agents

The Breast Cancer Prevention Trial (P-1:BCPT) is a hallmark trial in the area of chemoprevention—the first ever definitive demonstration of efficacy of a chemopreventive agent in a major cancer (37). The results of this randomized controlled trial (RCT), published in the Journal in 1998 (38), led to US Food and Drug Administration (FDA) approval of the selective estrogen receptor modulator (SERM) tamoxifen for risk reduction of breast cancer. The underlying hypothesis came from eight early-stage breast cancer adjuvant tamoxifen trials, summarized in the Journal in 1991 (39). Secondary endpoints from these RCTs provided evidence that tamoxifen reduced contralateral breast cancers by 35%, suggesting a possible role for this agent in primary prevention of breast cancer in women at elevated risk. Of four major randomized tamoxifen-vs-placebo prevention trials, the BCPT was by far the largest, with 13 388 women deemed at increased breast cancer risk (≥1.67% risk over five years), primarily determined by the original 1989 Gail model (24). A 49% decrease in invasive as well as noninvasive breast cancer incidence was seen with tamoxifen, confined to estrogen receptor (ER)–positive breast cancers (69% reduction). A seven-year analysis in the Journal confirmed a 43% decrease in invasive cancers and a 62% decrease in ER-positive cancers with tamoxifen (40).

Despite tamoxifen-related toxicities, endometrial cancer, and venous thromboembolic events (VTEs) (pulmonary emboli, deep vein thrombosis) (38), populations of women at sufficient risk for breast cancer were identified that are likely to have a net benefit. Another *JNCI* publication reported on associations of a tamoxifen-induced hypercoagulable state with genetic predisposition to clotting. In a nested case-control study in the 76 women with VTEs, no association of VTEs with either of two prothrombotic mutations in the genes encoding two coagulation factors, Factor V Leiden (FVL) and prothrombin G20210→A (PT20210) was observed (41). In contrast, risk was elevated (relative risk [RR] = 1.9) in women taking tamoxifen vs placebo and in women with higher vs lower body mass index. The risk of VTEs and endometrial cancer have discouraged widespread use of tamoxifen for risk reduction (42). A *JNCI* article addressing the issues related to the underuse of preventive tamoxifen involved The Sister Study prospective cohort of women without breast cancer but with a sister with breast cancer (43). While most women taking tamoxifen for chemoprevention were deemed likely to benefit, 20% of women taking the drug lacked sufficient evidence that its benefits would outweigh its risks. Furthermore, 46% of users had

discontinued tamoxifen before the intended five years, likely attenuating the potential effectiveness. An accompanying editorial pointed to the omission of certain very high-risk women (those with lobular carcinoma in situ [LCIS]) and the lack of ongoing systematic efforts to maintain adherence to prolonged chemopreventive therapy as possible contributing factors to the high discontinuation rate (44).

The Prostate Cancer Prevention Trial (PCPT) tested the ability of the 5α-reductase inhibitor finasteride for seven years to reduce the period prevalence of prostate cancer in 18 882 healthy men age 55 years and older (PSA ≤3 ng/mL, normal digital rectal exam [DRE]) (45). Prostate cancer diagnoses, made by "for cause" biopsies (PSA >4 ng/mL or suspicious DRE) or by preplanned end-of-study biopsies, revealed a 24.8% reduction in prevalence (P < .001) with finasteride vs placebo. Yet, more high-grade (Gleason scores 7–10) tumors were observed in the group randomly assigned to receive finasteride (37% of tumors, 6.4% of men) vs placebo (22.2% of tumors, 5.1% of men). This observation raised concerns about the safety of this otherwise effective chemopreventive agent, deterring the FDA from approving it (also dutasteride) for the repurposed preventive indication (46). Several explanations for the selective emergence of high-grade tumors with finasteride were explored in *JNCI* publications (47–50). One possibility is that reduction of prostate volume with finasteride led to disproportionate sampling of the gland ("increased sampling density") on fine needle biopsy. Modeling showed that sampling density bias could reasonably explain the excess of high-grade tumors in participants treated with finasteride (49). PSA sensitivity was also higher in the finasteride than the placebo group, increasing the likelihood of a biopsy and ultimate detection of all grades of tumors with finasteride (47). Another explanation holds that finasteride, which reduces PSA levels, did so to a lesser extent in participants who had incipient high-grade prostate cancer at the beginning of the study, biasing this group toward being biopsied (49). On histological exam of a subset of prostate biopsies from the two arms of the PCPT, Lucia et al. (50) concluded that finasteride did not directly influence tumor morphology. Rather, the differential in high-grade disease seen between the two arms at biopsy was reduced at prostatectomy, consistent with sampling bias introduced by a decrease in prostate volume and selective inhibition of low-grade cancers with finasteride.

Another key finding from the PCPT that was published in the Journal had important implications for using PSA to screen for prostate cancer. Both overall and high-grade prostate cancer were observed at study entry in men exhibiting the entire range of PSA levels, 0.0 to 4.0 ng/mL (45,47). The risk of each outcome increased progressively with PSA level (47). Among clinically significant cancers biopsied "for cause," 21.1% were associated with PSA levels between 2.6 and 3.9 ng/mL, similar to the frequency seen with PSA levels between 4.0 and 10.0 ng/mL (45). The continuous distribution of overall and high-grade prostate cancers in relation to PSA levels, without a discreet cutoff, raises concerns about the arbitrariness of using a 4 ng/mL threshold—or any threshold—as an indication for prostatic biopsy.

Prevention Trials Using Nutritional Agents

JNCI has long played a role in highlighting nutritional agents for prevention, both by global dietary manipulation and by intervening with distinct nutrients/bioactive food components.

Individual Nutrients/Bioactive Food Components

The Nutrition Intervention Trials in Linxian, China, a region with a high rate of esophageal/gastric cardia cancer and low intake of several micronutrients, studied dietary supplementation with combinations of eight vitamins and minerals, allotted according to a 2^4 factorial design (51–52). Companion reports in the Journal showed that among the 24 584 participants taking supplements, 32% of deaths were from esophageal/gastric cancer (51). In the general trial population (51), benefits were seen only with selenium, vitamin E, and beta-carotene on total mortality, mainly because of reduction in cancer mortality. Stomach cancer, with mortality reduced by 21%, was the major contributor to this reduction. Cancer incidence rates mirrored the cancer mortality patterns (52). Even 10 years after stopping supplementation, participants with baseline esophageal dysplasia in the selenium, vitamin E, and beta-carotene study arm had lower mortality (53).

Two key trials tested so-called antioxidant nutrients for lung cancer prevention: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (54–55) and the Beta-Carotene and Retinol Efficacy Trial (CARET) (56–57). Beta-carotene was used based on epidemiologic evidence suggesting low lung cancer risks in association with diets high in yellow, orange, and dark-green leafy vegetables and some fruits, which contain the plant pigment beta-carotene, a vitamin A precursor. In addition, individuals with higher serum beta-carotene levels exhibited lower risks of lung cancer in observational studies. Both trials recruited participants at high risk of lung cancer based primarily on smoking history.

The ATBC trial also used alpha-tocopherol (AT), the most abundant form of vitamin E, present in nuts, seeds, grains, vegetable oils, and other foods (54). Laboratory as well as epidemiologic evidence pointed to an association of this nutrient with reduced lung cancer risk. In this RCT, over 29 000 Finnish male smokers were randomly assigned by a 2 X 2 factorial design to four groups: AT, beta-carotene, AT + beta-carotene, or placebo for five to eight years. The initial analysis showed an unexpected 18% higher rate of lung cancer in men receiving beta-carotene vs those who did not. Delving deeper into these concerning ATBC results (55), *JNCI* publications reported that along with a higher incidence of lung cancer in beta-carotene users (RR = 1.16), this elevation with beta-carotene was somewhat stronger among heavy smokers (RR = 1.25) and in men with high alcohol intake (RR = 1.35). Supplementation with AT exerted no demonstrable effect on lung cancer risk (RR = 0.99) or on total mortality (54–55). A key secondary finding was a 32% decrease (95% confidence interval [CI] = -47% to -12%) in incidence of prostate cancer in men receiving AT compared with those who did not (58).

The CARET RCT, which tested the hypotheses that two vitamin A–related nutrients, beta-carotene and retinol, would decrease the risk of lung cancer, recapitulated the outcomes seen in ATBC. Random assignment of over 18 000 smokers, former smokers, and asbestos-exposed workers was to beta-carotene plus retinyl palmitate (retinol) or placebo for four years (56). The combination vitamins exhibited no benefit and possibly had an adverse effect on lung cancer incidence (28% more cancers) and all-cause mortality (17% more deaths), leading to early stopping of the trial (56). The Journal published results based on a prespecified analytic method (57), showing that lung cancer incidence and all-cause mortality were elevated with the intervention. The detrimental effects of beta-carotene and retinol persisted after drug cessation, as shown in a six-year follow-up report in the Journal (59).

The Nutritional Prevention of Cancer (NPC) trial tested the ability of selenium, a putative preventive agent, to reduce the incidence of new nonmelanoma skin cancer among 1312 individuals with a history of basal or squamous cell carcinoma of the skin who were residents of the southeastern United States, an area with low levels of soil selenium. In two reports, NPC failed to show that selenium decreased new skin cancer incidence (60–61). Secondary analyses of cancer outcomes in both NPC reports showed inverse associations between selenium treatment and the incidence of total lung, prostate, and colorectal cancer, as well as total cancer mortality. Strikingly, prostate cancer incidence was reduced with selenium supplementation (hazard ratio [HR] = 0.48, P = .005) (61), a finding that would lay the groundwork for a future prostate cancer prevention trial (see below). The benefit was most evident in participants with the lowest baseline plasma selenium concentrations (RR = 0.08, P = .002) (55,60).The underlying hypotheses and justification for the Selenium and Vitamin E Prostate Cancer Prevention Trial (SELECT) were introduced in a *JNCI* publication describing the planned study design (62). Selenium was chosen based on the reduction in incident prostate cancers, a secondary endpoint in the NPC trial (60), while vitamin E was chosen based on the secondary finding of a 32% decrease in prostate cancer incidence in men receiving AT in the ATBC trial (58). The selenium dose (200 µg/day) and the specific formulation, selenomethionine, were selected by a panel of selenium experts (62). In SELECT, 35 533 men age 50 years and older (African Americans) or age 55 years and older (all others) with serum PSAs of less than or equal to 4 ng/mL and nonsuspicious DREs were randomly assigned by factorial design to: selenium, vitamin E, selenium + vitamin E, and placebo. In contrast to the earlier preliminary evidence referred to above, no intervention group showed a reduction in prostate cancer compared with placebo (63–64). In fact, in a subsequent follow-up report, vitamin E supplementation was associated with a statistically significant 17% increased risk of prostate cancer (64–65). A recent *JNCI* article reported that selenium supplementation (selenium only and selenium + vitamin E arms) was associated with a 91% increased risk of high-grade prostate cancer among men with higher baseline selenium status (based on toenail selenium) but had no effect on men with low baseline selenium (65). Supplementation with vitamin E in SELECT was associated with increased risks of total (63%, P = .02), low-grade (46%, P = .09), and high-grade (111%, P = .008) prostate cancer in men with lower baseline selenium status (65).

Dietary Modification

The Journal has highlighted the value of studying behavioral interventions (diet, weight, physical activity) in clinical trials for cancer prevention or in the therapeutic setting (66–68). The Women's Intervention Nutrition Study (WINS), the first large-scale RCT to test such a lifestyle intervention (69), showed at 60 months follow-up a 24% lower risk of relapse in women with resected early-stage breast cancer assigned to a low fat-eating plan compared with those in the control group (P = .034). This overall benefit for the low-fat diet was shown by secondary analysis to be stronger in hormone receptor–negative breast cancers, a provocative and unexpected finding that begs explanation and replication. High-fiber and low-fat diets have been shown in some studies to be associated with a reduced risk of colorectal cancer or colonic adenomas. In several RCTs randomly assigning participants with a history of at least one resected colorectal adenoma or with familial adenomatous polyposis (FAP), fiber supplementation was associated with inhibition of

benign neoplasia (70–71). It remains to be seen whether this would translate into reduction in invasive cancer. Unlike fiber, hormone replacement therapy was shown not to be associated with reduced risk for overall adenomas in participants with a resected polyp in the Polyp Prevention Trial (PPT) (72), where random assignment was to a high-fiber diet or a control group (73). Finally, in another study, high-dose wheat bran fiber and calcium were associated with reductions in fecal bile acid concentrations suggesting a possible mechanistic link between reduction in colorectal neoplasia with these dietary interventions (74).

Cessation of Exposure to Carcinogens: The Case of Tobacco

Approximately 90% of lung cancers in the United States are causally linked to smoking, although fewer than 20% of smokers develop lung cancer (75). By identifying high-risk individuals, modeling to predict lung cancer risk enables cost-effective adoption of screening surveillance and other intervention programs. The Bach model (75) used prospective cohort data for smokers in the CARET trial to distinguish variability in absolute 10-year risk of lung cancer among smokers. For predictors, this model included age, sex, smoking history, and asbestos exposure. The Spitz model (76) used epidemiologic data (exposure to environmental tobacco smoke, family history of lung/smoking-related cancer, dust and asbestos exposure, history of respiratory diseases, smoking characteristics) from a case-control population to develop risk prediction models for never, former, and current smokers. More recently, lung cancer risk models with better performance characteristics have been reported using prospective data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (77).

Preventive interventions such as those used in the ATBC and CARET trials (55,57,59,78) have been disappointing and even shown detrimental effects (beta-carotene) in smokers (an important finding on its own). This leaves tobacco control as the main proven intervention for primary lung cancer prevention. Additional benefit should accrue to prevention of other smoking related cancers: cancers of the oral cavity, larynx, esophagus, pancreas, kidney, bladder, cervix, and stomach, and acute myeloid leukemia—to say nothing of a list of other common nonmalignant diseases such as cardiac disease and stroke. The psychoactive properties of nicotine make it difficult to quit smoking or achieve long-term abstinence without relapsing because of 1) nicotine dependence and 2) nicotine withdrawal symptoms. Nicotine is classified as an addictive drug comparable with cocaine and heroin.

Yet, many tobacco control initiatives in the United States have achieved success, reducing the prevalence of current smokers from 42% in 1965 to 19% in 2010. Behavioral therapy alone or in combination with pharmacotherapy can help smokers quit smoking. Decades ago, a large-scale NCI-funded intervention trial, the Community Intervention Trial for Smoking Cessation (COMMIT), that tested community intervention with existing resources found only a modest increase in quit rates for light-to-moderate smokers and no effect for heavy smokers (79). The results indicated the need for more intensive approaches, which may include pharmacotherapy. In the same timeframe, the NCI funded the American Stop Smoking Intervention Study (ASSIST) (80) in 17 states to develop tobacco prevention and control programs through policy-based approaches, with an objective of decreasing adult smoking prevalence. Unlike COMMIT, ASSIST states showed a small but statistically significant reduction in

smoking prevalence compared with non-ASSIST states. The study estimated that if implemented in all states, ASSIST would lead to a decrease in adult smoking prevalence of approximately 278 700 fewer smokers.

The Journal has prioritized research to develop antismoking strategies, for example to test the effectiveness of implementing guidelines provided by the Agency for Healthcare Research and Quality (AHRQ) (81). JNCI reports describe antismoking research targeted to special populations such as adolescents. Half of adolescent smokers have attempted to quit in the past year with a success rate of only 4%. Two 2009 JNCI articles reported an RCT that showed the efficacy of telephone counseling in combination with motivational interviewing for high school teen smokers (82–83). Another study investigated the benefits of a culturally sensitive intervention strategy for non–English speaking Asian immigrants. This RCT determined the effectiveness of multilingual quitlines for Asian (Chinese-, Korean-, Vietnamese-speaking) smokers and found that telephone counseling increased the six-month prolonged abstinence rates in all ethnic groups compared with self-help materials (84).

Medical treatment for smoking cessation includes nicotine replacement and non-nicotine pharmacotherapies, such as varenicline and bupropion sustained release (SR). Although enduring a higher burden of tobacco-related diseases, African Americans are often underrepresented in smoking cessation studies. In an RCT in African American light smokers (≤10 cigarettes/day), bupropion SR proved to be effective according to a biochemical confirmation method, but only during the medication phase of treatment, with no effect on long-term smoking cessation (85). Combination therapies may be even more effective than single-drug therapy. A positive screening result, whether CT scan or chest radiography, may also provide a wake-up call and motivate smokers to quit smoking. A recent JNCI study found a statistically significant association between smoking cessation and patient notification that they had screen-detected abnormalities in the National Lung Screening Trial (NLST) participants (86).

Conclusion

In addition to the hallmark 1998 publication of the BCPT, which by demonstrating a 49% risk reduction in breast cancer with tamoxifen, was the first major trial to document chemopreventive efficacy of any drug at any cancer site, the *Journal of the National Cancer Institute* has played a critical role in publication of follow-up analyses of outcomes from other large trials testing chemopreventive and nutritional interventions. Such post hoc analyses have provided insight into the biological underpinnings of carcinogenesis and chemoprevention. JNCI has provided a forum for analysis, even in the face of controversy, reflecting a strong commitment to the evidence-based advancement of cancer prevention and related areas of research.

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