Review

Cancer Epidemiology, Biomarkers & Prevention

The Surgeon General's Report on Smoking and Health 50 Years Later: Breast Cancer and the Cost of Increasing Caution

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Abstract

Despite the Surgeon General's strong track record and the rapidly expanding body of solid scientific work demonstrating that smoking caused a wide range of diseases, the decision making process for concluding "causality" in Surgeon General reports has become increasingly cautious and defensive. Whereas, the 1964 report did not conclude that smoking caused heart disease, it recommended that "from the public health viewpoint [one should] assume that the established association has causative meaning rather than to suspend judgment until no uncertainty remains," the *de facto* practice has become to do just the opposite. In particular, the 2004 report reached an affirmative negative conclusion that active smoking did not cause breast cancer and the 2006 report on passive smoking only found the link "suggestive." In contrast, in 2005 the California EPA found both active and passive smoking caused breast cancer in younger women. The evidence has continued to strengthen since 2005: there are now 12 large cohort studies that consistently demonstrate a dose–response relationship with smoking before first birth and increased breast cancer risk. The Surgeon General's increasing caution is preventing young women around the world from appreciating the risks that smoking and secondhand smoke pose for developing breast cancer. *Cancer Epidemiol Biomarkers Prev; 23(1); 37–46. ©2014 AACR.*

Introduction

The 1964 Surgeon General's report *Smoking and Health* (1), which is widely viewed as a precedent-setting document that legitimized and launched the U.S. government's efforts to reduce smoking (ref. 2, p. 237–8), also became the prototype for government-commissioned independent scientific reports designed to resolve controversies in science, medicine, and public health (ref. 2, p. 238). By design, the report did not break any new scientific ground: there was already a strong consensus among scientific authorities dating back at least 12 years, to 1952 when the International Union Against Cancer first concluded that increased smoking was associated with lung cancer in a dose-dependent way (ref. 3, p. 232). By 1954, the conclusion that smoking caused lung cancer had been expressed by Britain's Chief Medical Officer, Britain's Standing Advisory Committee on Cancer and Radiotherapy, the American Cancer Society and other national cancer societies. By 1962, the list had grown to include Britain's Medical Research Council, the Netherlands Ministry of Social Affairs and Public Health, Sweden's Medical Research Council, the Canadian Medical Association, British Royal College of Physicians, and World Health Organization (ref. 3, p. 232–5). Indeed, in 1957 then-U.S. Surgeon General Leroy E. Burney concluded that "excessive cigarette smoking is one of the causative factors in lung cancer" (ref. 3, p. 234).

Given this universal acceptance of the fact that smoking caused lung cancer, the obvious question is: Why was the 1964 Surgeon General's report needed at all? The answer, of course, is that it was designed to provide an "independent" authoritative assessment of the dangers of smoking in the face of the tobacco companies' aggressive campaign to cast doubt (4) on what, by normal scientific standards, would have been considered an overwhelming case that smoking caused lung cancer (and other diseases). This goal, combined with the tobacco industry's political power and aggressive attacks on any scientific statements implicating its products as causing disease, led to the U.S. government's unusual decisions to limit members of the Advisory Committee that was to write the report to people who had not taken any positions on smoking and health and to allow the Tobacco Institute (as well as the health organizations) to veto proposed members (ref. 3, p. 236). While often presented as a way to ensure "neutrality" on the Advisory Committee, this political

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decision denigrated actual scientific knowledge and experience and put the committee in an essentially defensive position from the beginning.

The result was an extremely cautiously written report that only concluded that "cigarette smoking is causally related to lung cancer in men" (ref. 1, p. 31). (The data "point[ed] in the same direction" for women; ref. 1, p. 31.) The report also noted a "relationship" between smoking and chronic bronchitis and emphysema," but not strongly enough to conclude causality and characterized smoking as a "habit" rather than an "addiction," largely due to the presence of Maurice Seevers, who had consulted for American Tobacco, on the committee (ref. 2, p. 220 and 223; ref. 3, p. 236–7) A Surgeon General report did not conclude that nicotine was addictive until 24 years later, in 1988 (5), 25 years after nicotine addiction was widely recognized—and used to design cigarettes—by the cigarette companies (4).

The 1964 report stopped short of concluding that smoking caused heart disease; nevertheless it concluded that the evidence was strong enough to warrant action:

> Although the causative role of cigarette smoking in deaths from coronary disease is not proven, *the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains* (ref. 1, p. 32). [emphasis added]

Based on this prudent assumption, the report went on to estimate that premature death from smoking-induced heart disease accounted for more deaths (32.9%–51.7% of excess deaths) than lung cancer (13.5%–24.0% of excess deaths; ref. 1, p. 317).

Between 1964 and 2004, the Centers for Disease Control and Prevention published 28 Surgeon General reports on a wide range of diseases and issues related to smoking. Except for the predictable attacks by the tobacco companies and their allies and fronts, these reports have been unchallenged. In 2004, noting that the 27 Surgeon General reports to date had used varying language to describe the linkages between tobacco use and disease (risk factor, association, cause) the CDC adopted 4 standard ways to describe the links between smoking and different diseases: causal, suggestive, inadequate to decide, and no causal relationship (ref. 6, p. 18).

Increasing Caution

Despite this strong track record and the rapidly expanding body of solid scientific work demonstrating that smoking caused a wide range of diseases, the decision making process for concluding "causality" in Surgeon General reports, which nominally maintained the same criteria as the original 1964 report, became increasingly cautious and defensive (7). For example, while addressing heart disease in the 1969, 1971, 1973, 1974, 1979, 1980, and 1983 reports, it was not until 1983—19 years after the 1964 report—that smoking became a "cause" of heart disease (ref. 6, p. 11).

An even more important reflection of increasing caution is the fact that, in contrast to heart disease in 1964, "causality" has become the *de facto* standard for recommending action. By the 2004 standard, the evidence linking smoking to heart disease would have been rated "suggestive." Thus, in stark contrast to the recommendation in the 1964 report that "from the public health viewpoint [one should] assume that the established association [between smoking and heart disease] has causative meaning," the *de facto* practice had become "to suspend judgment until no uncertainty remains."

Active and Passive Smoking and Breast Cancer

There is no better example of the impact of Surgeon General reports' growing caution than active and passive smoking and breast cancer. The Surgeon General's 2004 report (ref. 6, p. 312) reviewed the epidemiologic evidence published between 1992 and 2002 on active smoking, including 5 studies published between 2000 and 2002. The report concluded that, "Evidence for an increased susceptibility to the carcinogenic effects of cigarette smoking on the breast in subgroups of women (e.g., defined by genotype, menopausal status, age at starting smoking) has been inconsistent" (ref. 6, p. 312) and highlighted a 2002 meta-analysis that compared ever versus never smokers (8) that did not find elevated summary risk estimates for all cohort studies or all case–control studies (ref. 6, p. 312). The 2004 Surgeon General report stated that "hypotheses that women with higher levels of exposure to cigarette smoking (i.e., heavy smokers and those who have been smoking since an early age) would have elevated risks of breast cancer have not been supported by data from large studies" and that "[t]his null relationship is consistent with the 2 hypothesized mechanisms, antiestrogenic effects and carcinogenic exposures, that imply countervailing consequences of smoking that both increase and decrease the risk for breast cancer." Based on these conclusions the report reached the affirmative negative conclusion of "no causal relationship between active smoking and breast cancer" (ref. 6, p. 312).

From a logical point of view, it is important to recognize that such an affirmative negative conclusion is just as important as an affirmative positive conclusion. The Surgeon General report drove this fact home when it advised women, health professionals, and policy makers that "It would be false to tell women that they will prevent breast cancer if they quit smoking" (ref. 6, p. 312).

Despite the Surgeon General report's strong negative conclusion about active smoking, a year later, in 2005, the California Environmental Protection Agency, as part of evaluating secondhand smoke as a "toxic air contaminant" under California law, concluded that, "the weight of the evidence (including toxicology of tobacco smoke constituents, epidemiological studies, and breast biology) *is* consistent with a causal association between [secondhand smoke] exposure and breast cancer in younger, primarily premenopausal women" (ref. 9, p. 7–119). Evidence for older women was ruled "inconclusive" (ref. 9, p. 7–119).

Table 1. Summary risk estimates for breast cancer for ever regular secondhand smoke exposure in the 2005 California environmental protection agency and 2006 U.S. surgeon general reports

	California EPA Report		Surgeon General's Report	
	n	RR (95% CI)	n	RR (95% CI)
All studies	19	1.25 (1.08–1.44)	21	1.20 (1.08–1.35)
Premenopausal				
All studies	14	1.68[a] (1.31–2.15)	11	1.64[b] (1.25–2.14)
Studies with lifetime exposure assessment	5	2.20[a] (1.69–2.87)	6	1.85[b] (1.19–2.87)
Postmenopausal	9	[c]	10	1.00 (0.88–1.12)

Adapted from Collishaw et al. (71).

[a]Premenopausal women.

[b]Women less than 50 years.

[c]The California EPA did not report a summary risk estimate for postmenopausal women but noted that risk estimates from the 9 studies with data on postmenopausal women "cluster around a null association."

The pooled estimate of the relative risk was around 2, depending on which studies were used (Table 1).

In reaching this conclusion, CalEPA stressed the fact that the epidemiologic findings were congruent with what one would expect given what is known about the biology of breast cancer, including the identification of mammary carcinogens in secondhand smoke, demonstration of carcinogen-induced DNA adduct formation in breast tissue, the metabolic capability of mammary epithelium to biotransform carcinogens in smoke into active metabolites, and the demonstration that these compounds reach and damage human mammary tissue (ref. 9, p. 7–106 to 7–109).

In 2006, using a slightly different set of epidemiologic studies, the Surgeon General's report *The Health Consequences of Involuntary Exposure to Tobacco Smoke*, found essentially the same levels of risk of breast cancer in younger women associated with passive smoking (Table 1), but only found the evidence "suggestive," primarily because, of the 2004 Surgeon General report's affirmative negative conclusion about active smoking and breast cancer (ref. 10, p. 478–480). Rather than following the lead of the 1964 Surgeon General's report and using this conclusion of a "suggestive" link between passive smoking and breast cancer to recommend that women "assume that the established association has causative meaning" for purposes of prevention, the 2006 Surgeon General report recommended that, "while awaiting further evidence, women should be encouraged to avoid involuntary exposures to secondhand smoke because of the many adverse effects of inhaling secondhand smoke" (ref. 10, p. 480).

The 2006 Surgeon General's report devoted just one paragraph (ref. 10, p. 478) to the biologic evidence that would lead one to predict that tobacco smoke exposure would cause breast cancer and argued that the epidemiologic evidence justified discounting the biology (ref. 10, p. 478–9). In the end, the report made a decision against causality because, "the evidence that active smoking causes no overall increase in breast cancer weighs against a causal role for involuntary smoking" (ref. 10, p. 480).

The point is a reasonable one: If active smoking, which exposes women to much higher levels of carcinogens than passive smoking, does not cause breast cancer, how could passive smoking?

Why the Two Agencies Reached Different Conclusions

The difference between what the CalEPA and Surgeon General did is that the CalEPA went back and reassessed the evidence linking active smoking and breast cancer. In particular, CalEPA considered 23 epidemiologic studies published between 2000 and 2005, including the 5 published between 2000 and 2002 that the 2004 Surgeon General's report considered. The CalEPA examined risks in genetic subgroups [which an increasing number of studies were reporting (11–17)], examined risks for women with in higher exposure categories: early age of smoking initiation, smoking before first pregnancy, highest total years of smoking and total pack-years (11, 13, 18–29), and the effect on risk estimates for active smoking of controlling for passive smoking (30).

The CalEPA noted that a meta-analysis of 13 studies reporting active smoking risk controlling for passive smoking found a significantly elevated risk of 1.48 (95% CI, 1.17–1.86; ref. 30). In the 5 studies with a more complete passive exposure assessment, and thus cleaner referent groups, the breast cancer risk from active smoking was estimated at 2.08 (95% CI, 1.44–3.01; ref. 9, p. 7–78). Six prospective cohort studies published between 2002 and 2005 (22, 26, 28, 29, 31, 32) found statistically significant elevated breast cancer risk associated with active smoking for at least some of the metrics of exposure (ref. 9, p. 7–78).

As it did with passive smoking, CalEPA also devoted substantial attention to the biologic evidence that would lead one to expect that active smoking would cause breast cancer. Cal EPA listed 20 chemicals identified in tobacco smoke that the International Agency for Research on Cancer had identified as carcinogens that induce mammary tumors, including aromatic hydrocarbons such as

benzene and benzo[a]pyrene nitrosamines, and aliphatic compounds including urethane and vinyl chloride (ref. 9, p. 7–106) CalEPA noted that mammary epithelium is capable of metabolically activating carcinogens and concluded:

> The evidence with regard to plausibility of a causal association between environmental exposure to tobacco smoke and breast cancer thus includes the occurrence of identified carcinogens as components of [secondhand smoke], demonstration of carcinogen-DNA adduct formation in breast tissue, demonstration of metabolic capability of mammary epithelium to biotransform carcinogens such as PAHs to the active metabolite and demonstration that these compounds do, in fact, reach and damage human mammary tissue as a result of direct smoking or environmental exposures. This chain of evidence indicates that a causal association is highly plausible, both for active and passive smoking (ref. 9, p. B7–109).

Based on this analysis, CalEPA concluded that, "[c]onsidering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and breast cancer risk" (ref. 9, p. B7–79).

Active Smoking and Breast Cancer Risk Since the 2005 CalEPA Report

Because the primary reason for differences in conclusions about passive smoking between these 2 authoritative reports is the difference in the interpretation of the data on active smoking, we next consider studies published since May 2005, the date of the most recent paper reviewed in the CalEPA report. Increased risks for the 4 smoking metrics in Table 2 have continued to be reported in the newer literature for both case–control (33–52) and cohort studies.

We focus here on the large (>500 cases) prospective cohort studies examining women's smoking histories in more precise ways than the never/ex/current smoker measures of exposure used in the older studies. Cohort studies are less susceptible to selection and recall bias, which can be a concern in case–control studies. Larger cohort studies provide more precise and stable risk estimates, the ability to evaluate risk in subgroups and to examine dose–response.

Table 2 lists all cohort studies published as of October 2013 with at least 500 breast cancer cases that presented risk estimates for youngest age at smoking initiation, longest duration/highest pack-years of smoking before first birth, longest lifetime duration of smoking and/or highest total pack-years of smoking categories. These 4 measures have been identified (along with passive smoking) as the ones best for detecting an increased breast cancer risk associated with smoking (53). The 4 measures overlap in terms of exposure and only with recent large cohort analyses has there been clarification of their relative importance. All 12 of these large cohort studies report increased breast cancer risk in the highest exposure category for most of these metrics. The majority of the estimated risks are statistically significant. For example, 11 of 12 studies detected significant increases in risk for the women in the highest category of smoking before first birth.

Two meta-analyses, one published in 2004 (54) and one in 2011 (55), have compared risks for smoking before first birth or only smoking before first birth with smoking after first birth or only smoking after first birth. Both concluded there was no difference in risk for smoking before or after first birth. Although this may seem to be at odds with results presented above, it is actually an issue of precision—it is now apparent that smoking/not smoking is not a precise enough measure of exposure to observe a clear increase in breast cancer risk (56) primarily because the range of exposure can be large—from as few as 100 cigarettes ever smoked (the common definition of an "ever smoker") to decades of smoking 50 or more cigarettes a day. In contrast, the pooled estimate (using a random effects meta-analysis) of the relative risk for the highest category of exposure to smoking before first birth from the 12 large cohorts is significantly elevated: 1.30 (95% CI, 1.20–1.420).

The Critical Window of Active Smoking Exposure for Breast Cancer: Menarche to First Birth

Female breast tissue goes through 4 developmental stages of cell differentiation from birth, through puberty, childbirth, and lactation (57). Animal studies have shown that mammary cells are most sensitive to chemical carcinogens when they are between puberty and first birth and lactation. Rodents exposed to mammary carcinogens readily developed mammary tumors if they were exposed before they had a litter, while the same carcinogens introduced after the rodents had a litter produced few mammary tumors (58, 59). Thus, one would expect women who smoked (or were exposed to secondhand smoke) after menarche and before first birth to be at the highest risk whereas women exposed later in life to not be as affected by the tobacco smoke exposure, if at all.

In 2007, Ha and colleagues analyzing data from the U.S. Radiation Technologists cohort, were the first to provide strong evidence that menarche to first birth was the critical window for breast cancer risk from smoking and that the risk followed a dose–response relationship with pack-years of smoking during that time (60). In 2011, Xue and colleagues (61) replicated Ha and colleagues' findings using the Harvard Nurses' Health Study cohort with much larger numbers (8,772 cases). This study benefited not only from the large number of cases, but also from the precision of the smoking history that was based not only on the smoking status and history up to the time of recruitment (as is almost always the case in cohort studies), but also from collecting smoking behavior every 2 years since the cohort was established in the late 1970s.

Table 2. Cohort studies (>500 cases) of active smoking and breast cancer risk by highest exposure categories[a]

Reference	Cohort studied	No. of incident cases/no. in cohort	Highest pack-years or longest duration before first birth[b] RR (95% CI)	Youngest age[c] of initiation RR (95% CI)	Longest duration[d] RR (95% CI)	Highest pack-years[e] RR (95% CI)
Al-Delaimy (67)	Harvard Health Professionals Cohort	1,009/112,844	1.10 (0.80–1.52)	1.29 (0.97–1.71)	1.21 (1.01–1.45)	
Reynolds (29)	California Teachers Cohort	2,005/116,544	1.13 (1.00–1.25)	1.17 (1.05–1.30)	1.15 (1.00–1.33)	1.25 (1.06–1.47)
Gram (28)	Norwegian Cohort of Norway (CONOR)	1,240/102,098	1.27 (1.07–1.37)	1.48[f](1.03–2.13)	1.36 (1.06–1.74)	1.46 (1.11–1.93)
Olson (69)	Iowa Women's Health Study	2,017/41,836	1.21 (1.01–1.25)	1.12 (0.92–1.36)	1.18 (1.00–1.38)	1.15 (0.96–1.37)
Cui (70)[g]	Canadian National Breast Screening Study	4,445/89,835	1.13 (1.01–1.25)	1.11 (0.97–1.28)	1.50 (1.19–1.89)	1.17 (1.02–1.34)
Ha (60)	U.S. RadiologicTechnologists	906/56,042	1.78 (1.27–2.49)[h]	1.48 (0.77–2.84)		
Luo (68)	U.S. Women's Health Initiative	3,520/79,990	1.21 (1.11–1.33)[i]	1.12 (0.92- 1.36)	1.35 (1.03–1.77)	1.18 (1.02–1.37)
Xue (61)[j]	Harvard Nurses' Health Study	8,772/111,140	1.25 (1.11–1.40)[k]	1.04 (0.98–1.09)	1.15 (1.04–1.27)	1.27 (1.16–1.38)
Gaudet (63)	American Cancer Society Cancer Prevention II (CPSII) Nutrition Cohort	3,721/73,388	1.45 (1.21 - 1.74)[l]	1.23 (1.04 to 1.46)	1.28 (0.97 to 1.68)	
Bjerkaas (62)	3 National Norwegian cohorts	7,490/302,865	1.60 (1.42–1.80)[m]	1.30 (1.05–1.61)	1.31 (1.09–1.57)	1.34 (1.25–1.45)
Rosenberg (64)	The Black Women's Health Study	1,377/52,425	Pre 2.01 (1.10–3.65) Post 0.88 (0.55–1.39)	1.35 (0.97–1.88) 0.83 (0.58–1.17)		1.33 (0.86–2.05) 0.92 (0.66–1.30)
Dossus (65)	European Prospective Investigation into Cancer and Nutrition (EPIC) (10 European countries)[n]	9,822/322,988	1.73 (1.29–2.32)[o]	Ex 1.07 (0.94–1.23) Curr 0.96 (0.82–1.11)	Ex 0.99 (0.87–1.12) Curr 1.09 (1.02–1.17)	Ex 1.11 (0.97–1.27) Curr 1.11 (1.02–1.22)

Source: Adapted and expanded from the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (71, 75); Goodman et al. (76), Lawlor et al. (54), and Lin et al. (77) are not reported here because of small numbers of observed cases resulting in unstable risks and low statistical power (Goodman et al. only 21 smokers among the 156 breast cancer cases; Lin et al. only 12 ever smokers among 208 breast cancer cases; and Lawlor et al. reported 45 smokers before first birth among 139 breast cancer cases).

[a]All relative risks and 95% confidence intervals [RR (95% CI)] are relative to never (active) smokers unless otherwise indicated.

[b]All risk estimates based on smoking at least 5 years before first birth; except Gram et al. (28), Olson et al. (69), and Luo et al. (68) where years not reported.

[c]All risk estimates based on young women starting at age <20 years; cutoff varied from <15 to <20 depending on the study.

[d]All risk estimates based on smoking >20 years; with most women smoking >40 years.

[e]All risk estimates based on smoking >10 pack-years; with most women smoking >40 pack-years.

[f]Risk estimate based on ever smokers, who smoked 20+ years and started smoking at 10–14 years.

[g]Extended follow-up for same cohort as Terry et al. (26).

[h]Risk estimate based on 10+ pack-years of smoking before first childbirth after adjusting for smoking after first birth and other covariates, compared with not smoking before. The trend for smoking before first birth remained significant after additionally adjusting for age at smoking initiation.

[i]Risk estimate is for all women who started to smoke before their first full-term pregnancy. Comparison is among the 69,533 women who had at least 1 full-term pregnancy.

[j]Extended follow-up for same cohort as Egan et al. (22).

[k]Risk estimate based on ≥16 pack-years of smoking from menarche to before first birth, after adjusting for smoking in other life periods and 13 other risk factors.

[l]Risk estimate based on initiation of smoking after menarche, ≥11 years before first birth, among parous women.

[m]Risk estimate based on starting smoking more than 10 years before first childbirth.

[n]The EPIC cohort includes cohorts from 10 European countries with cohort entry varying by cohort between 1992 and 2000 and follow-up varying between cohorts from 2005 to 2010.

[o]Risk estimate is estimated increase for every 20 pack-years of smoking before first birth (P for trend = 0.0035), adjusted for smoking in other time periods. (Used because highest pack-year category before first birth was unstable due to small numbers.)

Like Ha and colleagues, Xue and colleagues found a dose–response relationship between pack-years of smoking between menarche and completion of the first full term pregnancy and increased breast cancer risk. Xue and colleagues reported relative risks, each statistically significant, of 1.11 (95% CI, 1.04–1.20), 1.19 (95% CI, 1.09–1.30), 1.21 (95% CI, 1.07–1.36), and 1.25 (95% CI, 1.11–1.40), for 1–5, 6–10, 11–15 and ≥16 pack-years of smoking before first birth (P for trend <0.001). This analysis controlled for multiple potential confounders *and* for smoking during other periods of life.

Four large cohort studies published in 2013 each found the highest risks for those women smoking the most before their first birth. Bjerkaas and colleagues (62) found a dose–response relationship between the number of years before first birth that a woman started smoking and increased breast cancer risk in a large study of 3 Norwegian cohorts. Women initiating smoking more than 10 years before their first birth had a 60% increase (HR = 1.60, 95% CI, 1.42–1.80) in breast cancer risk compared with never smokers (P for trend <0.001). Gaudet and colleagues (63) found a 45% increase in risk (RR = 1.45, 95% CI, 1.21 1.74) for women who started to smoke after menarche, but at least 11 years before their first birth in the large American Cancer Society Cancer Prevention II (CPSII) Nutrition cohort. Rosenberg and colleagues (64) found a doubling of premenopausal risk for women who smoked for at least 5 years before first birth and at least 20 pack-years in total in the U.S. Black Women's cohort, but no increased risk was observed for postmenopausal women. An analysis of the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort, the largest analysis to date with 9,882 breast cancer cases, found that pack-years of smoking between menarche and first birth is the strongest predictor of increased risk with an estimated risk increase of 1.73 (95% CI, 1.29–2.32) for every 20 pack-years (65).

Smoking, Breast Cancer, and Standard Criteria for Causality

The evidence that has appeared since the CalEPA report was published in 2005 has further strengthened the conclusion that active smoking causes breast cancer when the standards for causality are applied: strength, consistency, dose–response, temporality, coherence and biologic plausibility, and experimental evidence.

The evidence is strong and consistent. There are now 12 high quality cohort studies that have looked at detailed measures of smoking and breast cancer risk (Table 2). All 12 reported relative risks above 1 for the their highest category of years or pack-years of smoking before first birth category. Eleven of the elevated risks were statistically significant. Furthermore, the studies with the largest numbers of cases provided the clearest evidence of increased risk (61, 62, 65). These high quality cohort studies controlled for the major potential confounding factors and represent the prospectively tracked experience of more than 1.4 million women and more than 47,000 women who developed breast cancer. They include analyses of many of the major U.S. cohort studies including the American Cancer Society's Cancer Prevention II Cohort (66), the Harvard Nurses' Health Study Cohort (61), the Harvard Health Professionals' Cohort (67), the U. S. Radiologic Technologists Cohort (60), the U.S. Black Women's Cohort (64), the Women's Health Initiative Cohort (68), the California Teachers Cohort (29), and the U.S. National Cancer Institute's Iowa Women's Health Study Cohort (69), as well as the major European cohort—the European Prospective Investigation into Cancer and Nutrition (EPIC) involving collaboration of 10 European countries (65).

Eleven (28, 29, 60–65, 68–70) of the 12 cohort studies (28, 29, 60–65, 67–70) reporting on smoking before first birth demonstrate increased risk, and the weight of evidence suggests a dose–response relationship with duration or pack-years of smoking between menarche and first birth (56). Regarding temporality, the smoking of concern precedes the development of the breast cancer in all these studies. Regarding coherence, the isolation of highest smoking risk in the time between menarche and first birth, goes a long way to explaining why earlier studies (where many of the women may have started smoking after their first birth) failed to consistently find increased risk for ex or current smokers (8) and why current smokers or those with the longest lifetime duration or highest lifetime pack-years do not necessarily have the highest risks. And, as discussed above, the epidemiologic finding that the risks are highest for exposures to younger women is exactly what one would expect based on the biology (9, 57).

In addition to these traditional criteria for causality, an important criterion for assessing a causal conclusion for the link between smoking and breast cancer (or any disease) is the availability of a credible alternative explanation that simultaneously explains the full range of biologic and epidemiologic observations. Such an approach moves beyond assessing the potential limitations of each single study—after all, there is no such thing as a perfect study—to judge whether such a plausible alternative explanation exists. The 1964 Surgeon General's report did so when it explicitly rejected the "constitutional hypothesis" that the same genetic factors predisposed people to both smoking and lung cancer (ref. 1, p. 190–3). Failure to identify a competing plausible alternative hypothesis strengthens a causal conclusion.

A concern about confounding by alcohol has been raised as alcohol is a known breast cancer risk factor (8) and there is a correlation between alcohol use and smoking (8). However the 12 cohort studies presented above controlled for alcohol. In addition, in the large analysis that reported confounding of smoking by alcohol (i.e., among women who never drank there was no increase in breast cancer risk with smoking), ever/never smoking was used as the measure of smoking (8). When longest duration was used as the measure of smoking and alcohol controlled for in the same studies, a smoking risk was usually observed (ref. 71, p. 16–19). Furthermore, the

alcohol-breast cancer risk has been demonstrated as a risk with a linear dose–response curve, i.e. the more alcohol consumption the more risk (8). It has not been proposed as a risk affecting only the time before first birth. If alcohol confounded the smoking relationship one would expect that the largest smoking risk would be observed for total pack-years as that would correlate more closely to total alcohol consumption, than the amount of smoking before first birth. Finally, the large cohorts also observed *reductions* in risk for those women smoking the most after menopause and that would not be consistent with the smoking risk actually being an effect confounded by alcohol.

There is one major outstanding scientific question related to the effects of tobacco smoke exposure on breast cancer: Why are the observed risks for active and passive smoking not more different given the much larger dose of carcinogens that the active smoker experiences? The Surgeon General calculated a summary premenopausal breast cancer risk for passive smoking of 1.64 (95% CI, 1.25–2.14) for all 11 studies and 1.85 (95% CI, 1.19–2.87) for the 6 studies with lifetime passive exposure assessment, while the summary risk estimate we calculated for the highest exposure to active smoking before first birth was 1.30 (95% CI, 1.20–1.42) for all breast cancer. First, the passive smoking analyses found higher risk only in premenopausal women, but only 1 of the 12 active smoking cohort studies reported on premenopausal breast cancer. That cohort reported a doubling of risk for premenopausal breast cancer risk (RR 2.01; 95% CI, 1.10–3.65) and no increase in risk for postmenopausal breast cancer (0.88; 0.55–1.39; ref. 64). So it may be that premenopausal breast cancer is more sensitive to smoke and the apparent incompatibility may just be related to differences in which women are being studied for the passive and the active smoking. (It is generally difficult to get a large number of premenopausal breast cancer cases in a cohort study because premenopausal cancer represents only about 10% of all breast cancer cases.) Other possibilities are described by Miller and colleagues (57), Morabia and colleagues (72), and Vineis (73). The fact that this question remains unanswered is, however, not a reason to discount the strong and consistent evidence that both active and passive smoking increase the risk of breast cancer in women.

Implications

One can understand the extreme caution that the Surgeon General's Advisory Committee had in 1964. The tobacco companies were in full attack mode. Since then, however, there have been 2 important changes. First, the credibility of the scientific process has withstood the test of time in that not a single conclusion about the dangers of smoking and other tobacco use have been reversed. Indeed, as more evidence has accumulated, the pattern has repeatedly been that the risks are higher than originally thought, both in terms of magnitude and the range of diseases tobacco causes. Second, a federal court has found (74) and the Supreme Court allowed to stand a judgment that the major cigarette companies have been found to have been (and likely to continue to be) engaged in a massive conspiracy to defraud the public under the Racketeer Influenced Corrupt Organization Act. The cigarette companies remain under the jurisdiction of a federal judge who has prohibited the companies (and their

Table 3. Smoking is shifting from males to females around the world[a]

	Prevalence ratio		Prevalence (%)					
			Females			Males		
	Girls/boys	Women/men	Girls	Women	Difference	Boys	Men	Difference
Argentina	1.4	0.7	21.3	23.5	2.2	15.1	34.3	19.2
Chile	1.4	0.7	40.0	30.7	−9.3	28.0	41.7	13.7
USA	1.1	0.8	13.9	21.6	7.6	12.1	26.3	14.2
India	0.3	0.04	1.6	1.0	−0.6	5.4	27.6	22.2
China	0.1	0.06	0.6	3.7	3.1	5.6	59.5	53.9
Philippines	0.5	0.2	12.0	8.4	−3.6	23.4	38.9	15.3
Ghana	0.8	0.07	2.3	0.5	−1.8	2.8	7.1	4.3
South Africa	0.5	0.3	10.6	7.8	−2.8	21.0	25.0	4.0
Uganda	0.7	0.08	4.2	1.5	−2.7	5.7	18.4	12.7
Jordan	0.5	0.2	7.1	9.8	2.7	13.2	61.9	48.7
UAE	0.3	0.06	3.6	1.6	−2.0	12.1	25.8	13.7
Bulgaria	1.3	0.6	31.7	27.9	−3.7	24.4	47.5	23.1
Russia	1.2	0.4	27.4	26.6	−0.9	23.3	70.1	46.8
Median	0.7	0.2						

[a]Adapted from an analysis prepared by Derek Yach based on data from the Global Youth Tobacco Survey (78).

agents) from questioning the dangers of smoking and secondhand smoke.

The issue of smoking and breast cancer is of more than academic interest. As the tobacco industry has expanded globally into the developing world, girls have been taking up smoking faster than boys, which is reflected in the facts that the ratio of smoking prevalence among girls to women is higher than that of boys to men in many low and middle income counties, with smoking prevalence among girls sometimes exceeding that of women whereas smoking among boys is always substantially below that of men (Table 3). It would be more compelling to these girls to warn them that smoking and passive smoking cause breast cancer, particularly when they are exposed while they are young, than advising them to avoid smoking and secondhand smoke for other reasons "while awaiting further evidence" (ref. 10, p. 480).

Of course one could make the argument that the extreme and growing caution that the Surgeon General reports have exhibited is the very reason for their credibility. In statistical terms the established practice has been to focus on the lower 95% confidence bound of risk to ensure that smoking is *at least* as bad as the Surgeon General says. While this may protect the authors from ever overstating a case, it is not a health protective standard. A more appropriate approach would be to focus on the upper 95% confidence bound and estimate the *maximum plausible risk* and use that to guide policy making. This is essentially what the 1964 Advisory Committee did when they told the public not to wait until "no uncertainty remains" and "assume that the established association has causative meaning" for heart disease.

The real question is who should assume the risk of an (unlikely) mistake by the Surgeon General, the tobacco companies who would stand unjustly accused of causing breast cancer or the public and public policy who would be deprived of timely adequate warnings?

Meanwhile, the Surgeon General continues to advise young women, "It would be false to tell women that they will prevent breast cancer if they quit smoking" (ref. 6, p. 312).

Who does that protect?

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.A. Glantz, K.C. Johnson
Development of methodology: S.A. Glantz, K.C. Johnson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.A. Glantz, K.C. Johnson
Writing, review, and/or revision of the manuscript: S.A. Glantz, K.C. Johnson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.C. Johnson
Study supervision: S.A. Glantz

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