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EDITORIAL

Cigarette smoking, cytogenetic abnormalities, and acute myelogenous leukemia

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Government advisories warning of the ill-effects of using tobacco products date back at least to the proclamation of James I of England (James VI of Scotland) (1566–1625), who in 1604, the year he commissioned the King James version of the Bible, described their use as 'A custome lothsome to the eye, hatefull to the Nose, harmefull to the braine, dangerous to the Lungs, and in the blacke stinking fume thereof, neerest resembling the horrible Stigian smoke of the pit that is bottomlesse'.[1] Although published anonymously, there was apparently little doubt about the author of those remarks, the King of England. The King also required Thomas Earle of Dorset, High Treasurer of England, to collect a tax on each pound of tobacco imported. It is said that when the royal exchequer grew from the tobacco tax imposed on imports from the Virginia colony, James's criticism of using tobacco products became muted. In any event, ascribing one more disease, acute myelogenous leukemia (AML), to the effect of smoking on its victims may add little to the substantial arguments that already exist for abstention.

The relationship of cigarette smoking to the incidence of AML was suspected in the 1970s and the studies alluding to this relationship were commented on in a Department of Health, Education and Welfare report on Smoking and Health in 1979. In 1986, the evidence for the association was reviewed and considered to be inconclusive.[2]

Although an association of cigarette smoking and AML has not been a universal finding in the studies on this topic, the majority of studies in the last 20 years have reported a statistically significant, moderate relationship (reviewed in Thomas *et al.*[3] and Brownson *et al.*[4]) with a relative risk of about 1.4 for AML among cigarette smokers compared to non-smokers and the relative risk approaching 2.0 for heavy smokers.[3,4] In 2004, the Surgeon General of the United States[5] and the International Agency on Research in Cancer of the World Health Organization,[6] each concluded, based on the data available, that cigarette smoking caused AML. Studies measuring population-attributable risk, the proportion of all cases of AML that can be attributed to cigarette smoking, have reported values ranging from 14 to 31%.[3,4,7–9] If the lowest value is true, cigarette smoking would be the most prevalent exogenous cause of AML. The risk of clonal cytopenia and oligoblastic myelogenous leukemia (myelodysplastic syndrome) has also increased in cigarette smokers, as would be expected given that these are more slowly progressive forms of AML.[10,11] Cigarette smoking has also been associated with shorter remission and survival durations and more pulmonary infections during the period of severe pancytopenia induced by therapy of AML.[12]

There has also been interest in the relationship of paternal or maternal smoking before or during pregnancy to the incidence of acute leukemia in the child. Conflicting results of these relationships have been published, including a relationship to paternal smoking,[13] maternal smoking[14] and no relationship to parental smoking.[15,16] Some studies found a relationship with childhood acute lymphocytic leukemia (ALL),[13,17,18] some with childhood AML[14,19] and occasionally with both acute leukemias.[20] Because the genotoxic effects of cigarette smoke on susceptible lymphohematopoietic cells appear to be relatively weak, additional appropriately-designed studies would be needed to settle the question of parental smoking and acute leukemia.[21] The evidence for the initial mutation occurring in utero in some cases of childhood ALL[22] makes this relationship worthy of conclusive study.

The following three additional unresolved questions have developed from the studies of cigarette smoking and adult AML: (1) What is (are) the leukemogen(s) in cigarette smoke? (2) Is the effect of the leukemogen(s) transduced more commonly through mutations involving chromosome 7 and 8 than other chromosomes, for example chromosome 5, the latter, along with chromosome 7, known to be among the two most prevalent chromosomal abnormality in chemotherapy-induced AML?[23] and (3) Is a particular phenotype of AML more prevalent in smoking-associated AML than in *de novo* AML?

Unlike the oral and nasal cavities, the laryngotracheobronchial tree, and perhaps the upper gastrointestinal tract, which receive high concentrations of tobacco smoke, and the kidney and urinary bladder, which receive high concentrations of carcinogenic tobacco smoke metabolites, the sites harboring susceptible lymphohematopoietic cells would be subject to concentrations of smoke-containing mutagens present in blood and body fluids. Thus, the genotoxic dose derived from tobacco smoke would be expected to be relatively low compared to sites directly in contact with cigarette smoke. However, given the strong addictive effect of nicotine in tobacco, the duration of the exposure often would be long.

The smoke of combusted tobacco is estimated to contain over 3800 chemicals of which over half are considered potential toxins or carcinogens.[24] Studies of the genotoxic effect of mainstream cigarette smoke and cigarette smoke condensate have verified that they induce an increase in micronuclei formation and in chromatid exchange in lymphocytes and myeloid tissues. One focus of the link between smoking and leukemia has been on the content of benzene in tobacco smoke,[25–29] although numerous other potential toxins in cigarette smoke are also candidates.[24,30–32] Benzene exposure in an occupational setting, if over a threshold concentration–time exposure (e.g. 20–40 ppm-years) is a documented cause of AML. The threshold level of benzene that is leukemogenic is not precisely known.[33,34] Susceptibility may also be influenced by polymorphisms in detoxifying enzymes.[35] The general population is exposed to benzene principally through active and passive cigarette smoking, the emissions from motor vehicles exhausts and the atmospheric content around gasoline stations.[34] Personal exposure assessment research has indicated that an average cigarette smoker inhales 6–10 times the benzene inhaled by an average nonsmoker, and that approximately 90% of a smoker's benzene exposure is from smoking.[26,28]

The benzene metabolites, catechol and hydroxyquinone, are increased about 80% and trans-muconic acid about 40% in the urine of smokers as compared to non-smokers.[29] Benzene metabolism is complex and incompletely understood.[33] Meta-

bolites of benzene derived initially from liver enzyme action (e.g. catechol and hydroxyquinone) are surmised to be converted to toxic derivatives in the marrow, based on studies in animals and of isolated lymphohematopoietic cell (including CD34-positive marrow cells); and, in the marrow they are responsible for inducing DNA damage and impairing DNA repair in hematopoietic cells.[33] Although the concentration of specific genotoxic derivatives of benzene in marrow has been disputed, acute myelogenous leukemogenicity is not in dispute, which is based on the numerous epidemiological studies of industrial populations.[33,34]

The possible role of benzene in cigarette smoke to the induction of AML was questioned in an early report, when the authors considered the occupational exposure to benzene as a requirement to increase rates of AML. These authors concluded that the amount of benzene in cigarette smoke probably would not explain a relative risk, which is twice that of the non-smoker.[2] In a more recent report, the investigators estimated that the lifetime exposure of benzene in cigarette smoke contributed 12–58% of all smoking-related AML deaths.[28] If so, one would infer that benzene is an important but not sole contributor to smoking-associated AML. The effect of cigarette smoking on death from other cancers and from heart and lung diseases, which are the dominant smoking-induced causes of death, may leave a residual population of smokers, some of whom would die of AML and a proportion of whom may be principally affected by benzene exposure in cigarette smoke.

Several studies have examined the relationship of cytogenetic abnormalities to patients with AML who were cigarette smokers. Table 1 summarizes the cytogenetic findings in cigarette smokers with AML. Most striking is the frequency of reports of abnormalities of chromosome 8, especially trisomy 8[36,37] and *t*(8;21)[36,38] and of chromosome 7.[39–41] One report found an association of AML with chromosome 5 abnormalities in patients who smoked cigarettes.[36] Although the data are insufficient to reach firm conclusions, the apparent relative frequency of associations with chromosome 8 is in contradistinction to data on chemotherapy-associated AML.[42] Studies of the effect of benzene metabolites on cells in culture[43–47] and of cases of AML linked to industrial exposure to benzene[48–50] have found that loss of all or part of chromosomes 5 and 7 and gain or loss in chromosome 8, or *t*(8;21)) are the prevalent changes. The similarities to the chromosome abnormalities found in smoking-associated AML, however, cannot be considered a basis to make the connection between smoking-associated AML and benzene, since abnormalities in 5 and 7 are

Table 1 Cytogenetic abnormalities in AML/MDS patients who were smokers

Population studied	*Cytogenetic findings*	*Comments*	*Reference*
472 patients with AML in England. Examined the odds of being a smoker with AML and having a specific cytogenetic abnormality.	*t*(8;21) only abnormality that correlated with smokers with AML. OR = 4.8 (CI = 1.8–13) for 'ever smoked' versus 'never smoked'; OR = 7.0 (CI = 2.6–19) for 'current smoker' versus 'never-smoked'	No statistically significant association with other cytogenetic abnormality.	Moorman *et al*. [38]
168 patients with AML in Sweden who were smokers had their cytogenetic abnormalities compared to 166 patients with AML who were non-smokers.	No significant difference in the categories of cytogenetic changes between the two groups.	OR = 2.2 (CI = 0.80–6.2) for smokers compared to non-smokers with −7 or 7q- but not statistically significant. Acute erythroleukemia and acute monocytic leukemia more prevalent among smokers. Very small numbers, however.	Bjork *et al*. [40]
330 patients with MDS in Sweden	Chromosome 7 abnormalities associated with smoking. OR = 5.0 (CI = 1.5–23) (especially −7/7q-). OR = 2.4 (CI = 0.61–9.3) for association with chromosome 8 but not statistically significant.	Cigarette smoking more closely associated with clonal anemia (refractory anemia) than oligoblastic myelogenous leukemia (RAEB) and AML (RAEB-t).	Bjork *et al*. [41]
79 patients with AML/MDS in Italy	Patients with AML who were smokers had an increased frequency of chromosome 8 abnormalities (especially +8) compared to non-smokers OR = 6.3 (CI = 0.9–42). If limited to smokers of ⩾10 cigarettes per day, OR = 14 (CI = 1.4–142).		Davico *et al*. [37]
84 patients with AML with acute myeloblastic leukemia with or without maturation (excluded other phenotypes) in United States	Patients divided into NN vs AA/AN groups. Cigarette smoking associated weakly with propensity to have abnormal cytogenetics. The greater the number of cigarettes smoked the greater the likelihood.	Relatively small number of patients. Compare the results against their prior series of patients (No. = 129). OR for specific cytogenetics abnormality among smokers with AML vs non-smokers with AML in the two series were similar: OR = 1.5 and 1.5 for 5-/5q-, OR = 2.1 and 1.6 for +8 and OR = 1.7 and 2.4 for *t*(8;21).	Crane *et al*. [36]
378 patients with AML in United States and Canada	Frequency of −7/7q-, +13, and −Y were increased in cigarette smokers with AML compared to non-smokers with AML. The relationship with −7/7q-, −Y and +8 was stronger in patients with the two subtypes: AML with and without maturation.	Smokers ⩾60 years had increased risk of AML, OR = 2.0 (CI = 1.2–3.3). Cigarette smoking was associated with ALL in patients ⩾60 years of age OR = 3.4 (CI = 1.0–12).	Sandler *et al*. [39]

Abbreviations: AA, all metaphases examined with cytogenetic abnormality; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; AN, cytogenetic abnormality but admixed with normal metaphases; CI, confidence interval; MDS, myelodysplastic syndrome; NN, no cytogenetic abnormality; OR, odds ratio.

frequent in other cases of chemically (chemotherapy)-induced AML. The similarity between cigarette smoking-associated AML and occupational benzene exposure-induced AML in the prevalence of chromosome 8 abnormalities, likewise is not a conclusive finding.

A relationship of the phenotype of AML in those patients who are cigarette smokers has been examined looking for subtypes that are over- or underrepresented in smokers. Once again, insufficient study does not permit firm conclusions on whether one or another phenotype is more prevalent among cigarette smokers. Also, studies have been limited by total number of AML cases, which after stratification into subtypes, leaves fewer number of observations. Several studies have found a significant predominance of AML with maturation.[51,52] A study of 412 cases of AML diagnosed between 1987 and 1994 in Los Angeles County, California, found a modest overall risk of AML among smokers (OR = 1.2, confidence interval (CI) = 0.9–1.6). When stratified by AML subtype, patients with AML with maturation were more likely to have smoked (OR = 2.3, CI = 1.1–4.4) and if patients aged more than 60 years with AML with maturation were examined, they were even more likely to have been smokers (OR = 3.3 CI = 1.1–10). In patients with AML with maturation, the association with smoking was related to the number of cigarettes smoked per day and duration of cigarette smoking. These investigators estimated that 42% of patients with AML with maturation had smoking-induced leukemia.[51]

Cancer and Leukemia Group B, a multi-institutional cooperative cancer treatment group in the United States and Canada, investigated the leukemia risk associated with cigarette smoking in 610 adults, aged 18–79 years, with newly diagnosed acute leukemia.[52] Patients were classified by subtype of acute leukemia. The odds ratio for risk of acute leukemia associated with smoking controlled for age, race and sex was 1.1 (0.89–1.4). However, in patients $\geqslant$60 years with AML, the OR was 2.0 (CI = 1.2–3.3). Among patients $\geqslant$60 years, the risk increased with an increase of cigarettes per day smoked. When examined by subtype of AML, risk for AML with maturation increased at all ages: OR = 1.7 (CI = 1.0–2.9) for patients $<$60 years and OR = 3.5 (CI = 1.5–8.0) for those $>$60 years of age. This study also found an association between cigarette smoking and ALL in adults $\geqslant$60 years of age. In these two studies, the OR for smokers $\geqslant$60 years having AML with maturation compared to non-smokers was 3.3 and 3.5, respectively. Although the first study cited[51] found chromosome 8 abnormalities to be the most prevalent in cigarette smoking-associated AML, the latter study[51] did not. In another study, acute erythroleukemia was associated with cigarette smoking but the case numbers were quite low.[40]

Cigarette smoking as an environmental cause of AML merits additional study. The development of further knowledge regarding the leukemogen(s) involved, whether the leukemogen(s) has a propensity to induce a specific phenotype, and the underlying genetic determinants of such an association would be of pathobiological interest. The seeming predisposition to abnormalities of chromosome 8 and to AML with maturation, each associated with the other in *de novo* AML, is titillating but far from conclusive. Future studies of sufficient statistical power to answer these questions would be useful. These questions represent a challenge and an opportunity to the international cooperative groups studying AML.

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