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Investigation into the risk of ultra-low tar cigarettes and lung cancer☆

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ABSTRACT

We present analyses relating cigarette type to lung cancer based on a case-control study in five European countries. The analyses involved 3561 cases and 2301 controls with diseases not associated with smoking. Subjects completed a detailed questionnaire, including a lifetime smoking history. Analyses included never smokers, and those who smoked for at least 80% of the "critical period" from 2 to 20 years before diagnosis, ignoring those who ever smoked pipes or cigars, or chewed tobacco. The main analysis compares risk in those who, in the critical period, smoked ultra-low tar (ULT) cigarettes (machine yield ≤3 mg tar/cigarette) for 8 + years, with those who only smoked full flavour (FF) cigarettes (≥10 mg tar/cigarette). After adjustment for sex, age, country, education, age of starting smoking, mean cigarette consumption and mean tar level 21–50 years before interview, the odds ratio (OR) was 0.73 (95% confidence interval (CI) 0.50–1.06). Other analyses showed a modest, not statistically significant, reduction in risk with tar reduction. Risk in ULT smokers for 8 + years was substantially higher than in never smokers (OR 16.27, 95% CI 10.14–26.09). The study was prematurely terminated due to cost overrun, limiting the power to detect an association. More evidence is needed, particularly on lifetime ULT smoking.

1. Introduction

It has been known for many years that cigarette smoking causes lung cancer, and that the risk rises with increasing number of cigarettes smoked per day and with increasing duration of smoking (International Agency for Research on Cancer, 2004; Lee et al., 2012; US Surgeon General, 2014). The observed dose-response relationship of daily amount smoked to risk of lung cancer led to the suggestion (Wynder, 1957; Wynder et al., 1957) that more effective filtration could be one of a number of measures that might reduce the risk. Since then cigarettes on the market have changed from being predominantly plain to predominantly filter, and tar levels per cigarette have massively reduced (Forey et al., 2006–2016; US Surgeon General, 2014).

Whether this has actually helped to reduce lung cancer risk has been under discussion for many years. It has been pointed out (National Cancer Institute, 2001; US Surgeon General, 2014) that smokers switching to cigarettes with a lower tar or nicotine delivery as measured by smoking machines may, in an attempt to maintain their nicotine dose, "compensate" by smoking cigarettes more intensively and/or increasing the number of cigarettes smoked per day. However, a detailed investigation of the evidence suggests that though these forms of compensation may substantially reduce the benefit of switching to lower tar products, they do not eliminate it.

That there appears to be some benefit of switching to lower nicotine yield products can be demonstrated in various ways. Firstly, using an index in which 1 indicates complete compensation and 0 no compensation, Scherer and Lee (2014) combined evidence from 19 brand-switching studies to give an overall estimate of the compensation index of 0.781 (95% confidence interval [CI] 0.720 to 0.842). Based on this formula, a smoker switching to a cigarette with a 25% lower nicotine yield, as measured under standard smoking conditions, would, as a result of the considerable degree of compensation, only expect to be exposed to a 6% lower nicotine dose. Similarly, switching to a cigarette with a 50% lower machine yield, would only lead to a 14% decrease in dose.

Second, various reviews of the epidemiological evidence (Kabat, 2003; Lee, 2001; Lee et al., 2012; Lee and Sanders, 2004) have demonstrated a reduction in risk of lung cancer in smokers of filter compared to plain cigarettes and in smokers of lower tar compared

Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; FF, full flavour; LT, low tar; ULT, ultra-low tar; RR, Relative risk.

☆ This paper is dedicated to the memory of the late Dr Edward ("Ted") Sanders. The study described here was his idea, and he played a major role in getting it started.

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to higher tar cigarettes. The latest of these reviews (Lee et al., 2012), reported a 31% reduction in risk (95% CI 22%–39%) in "only filter" vs "only plain" cigarette smokers, with a 30% reduction in risk (95% CI 15%–42%) comparing smokers in the lowest vs highest tar groups. As also noted in an earlier review (Lee and Sanders, 2004) the benefit of reduction in yields was evident regardless of whether estimates were adjusted for daily cigarette consumption. Whether or not estimates should be adjusted is not in fact totally clear. Thus, if increased consumption is an effect of the reduction in nicotine yield, to do so might be considered over-adjustment (National Cancer Institute, 2001); however, if lighter smokers tend to be more likely to switch to lower yield cigarettes, not to do so might be considered under-adjustment.

While the latest review (Lee et al., 2012) was limited to studies published in the 1990s, a number of subsequent studies have tended to confirm the reduction in lung cancer risk associated with reduction in yields (Agudo et al., 2000; Brooks et al., 2003; de Stefani et al., 2002; Harris, 2004; Marugame et al., 2004; Papadopoulos et al., 2011; Simonato et al., 2001; Woodward, 2001), the only exceptions being where estimates have a wide 95% confidence interval (Blizzard and Dwyer, 2003; Rachtan, 2002).

Although the epidemiological evidence appears to confirm a reduction in lung cancer risk, it is subject to various limitations. Thus: (a) much of the evidence relates to comparison of smokers who have used reduced yield cigarettes for only a moderate proportion of their smoking lifetime; (b) some studies base results only on the brand smoked at one point in time or over a limited period; (c) lifetime histories are subject to errors in recall, particularly when respondents cannot recall brand names; and (d), as indicated above, it is difficult to make precise adjustment for those aspects of smoking which may be affected by a switch in the product smoked. One would really like to adjust for smoking habits measured pre-switch, but this is rarely if ever done.

A major problem with the evidence is that much of it relates to cigarettes with tar yields that are not currently on the market, and which may not be relevant to cigarettes with tar yields of less than 10 mg tar. Notably, none of the evidence on risk relates to the smoking of ultra-low tar (ULT) cigarettes, cigarettes which are defined as having a machine yield of 3 mg or less tar per cigarette. ULT cigarettes have become increasingly popular in the last 30 years.

The objective of this paper is to present results from a case-control study which was principally aimed at comparing lung cancer risk from smoking ULT cigarettes with that from smoking full flavour (FF) cigarettes, cigarettes with a machine yield of at least 10 mg tar. However, some other results, including those relating to smoking low tar (LT) cigarettes with a machine yield intermediate between ULT and FF cigarettes, are also presented.

This study, sponsored by Philip Morris International, was originally aimed at recruiting 13,000 cases and 13,000 controls, the large number of subjects being necessitated by the relatively low uptake of ULT cigarettes. Subject recruitment was initiated in December 2005, and continued until the sponsor discontinued support in October 2008 due to a substantial cost overrun. Though, at that time, detailed data were only available for about 30% of the planned sample, the numbers of cases and controls for which information was collected still make it one of the largest lung cancer case-control studies ever conducted.

Though a report on this study has already been made publicly available on the Philip Morris International website (Weinberg, 2013; provided as Supplementary File 1), this only presents results which relate average tar yield to lung cancer risk. While that report concluded that "average cigarette tar yield is an independent risk factor for lung cancer above and beyond the effects of smoking duration and smoking intensity", no results specifically relating ULT cigarette smoking to lung cancer risk were presented. Though we recognize that the premature termination of the study affects the precision of the risk estimates for ULT cigarette use, we feel it important to present the results relating to the original objective.

2. Materials and methods

2.1. Study design

As the methods by which the case-control study was conducted have been described earlier (see Supplementary File 1), only a summary of these is given below.

The study was conducted in France, Germany, Greece, Italy and Slovenia, countries selected because market penetration of ULT prior to the study launch was relatively high. The study involved recently diagnosed, medically confirmed primary lung cancer and controls with an admission diagnosis not associated with smoking. Histological type of lung cancer was not routinely recorded. Though the study design involved individual matching of controls to cases by age (±5 years), sex and area of residence, the early study termination meant that pairing was often incomplete, so the data were analysed as if unpaired. All subjects considered signed the informed consent form, had a score of 18 or above on the Standardized Mini-Mental State Examination (Vertesi et al., 2001), and completed a specifically designed Life Event History Calendar questionnaire, a data collection instrument that provided a framework of important events from the subject's own life history to aid the subjects' recall of past smoking habits (Belli, 1998; Belli et al., 2001). The smoking data included information on the number and brand of cigarettes smoked each year from the first year in which at least 100 cigarettes were smoked until 24–36 months prior to the date of signing the informed consent. Exclusion of recent smoking data sought to limit problems arising from smokers quitting or changing brands because they were ill prior to the lung cancer diagnosis. For each brand, tar yields were extracted from a Philip Morris database providing data from 1979. For earlier years, tar yields of 13 mg per cigarette were imputed. Missing data on amount smoked, and tar yield were imputed as described elsewhere in Supplementary File 1. The questionnaire also collected information on a range of demographic variables and exposure to other lung cancer risk factors.

At each time point it was possible to calculate from the smoking histories whether a subject then smoked and, if so, how many of each type of cigarette (ULT, LT or FF) were smoked, and hence the percentage smoked by type. If the percentage for any one type was greater than or equal to 70% the subject was declared to be a smoker of that type of cigarette in that year. If no type was smoked for at least 70% in the year they were declared to be a mixed cigarette smoker in that year.

2.2. Analysis

Analyses concentrated on the effects on lung cancer risk of smoking during the "critical period" from 2 to 20 years before diagnosis, as sales of ULT cigarettes before that period were negligible or non-existent in all the five countries involved. Never smokers were excluded from all analyses except those specifically involving never smokers. All analyses ignored smoking habits recorded in the year before diagnosis. Excluded from all analyses were those who had ever smoked cigars or pipes or chewed tobacco, those who had smoked for less than 80% of the "critical period" from 2 to 20 years before diagnosis, and the very few subjects who were mixed cigarette smokers throughout the critical period.

Various comparisons of risk in smokers were made: