ANNEX C

Proportion of lung cancers occurring among never smokers

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1. Introduction

At a recent meeting there has been some discussion about the proportion of total lung cancer cases which occur among never smokers. Results were quoted from Dijon and from Paris of, respectively, 1% and 6.8% and the question arose as to whether these percentages were in any way unusual. The proportion is obviously of importance when one comes to design new studies of ETS and lung cancer among never smokers. This note summarises relevant data from a number of studies - it is not intended to be comprehensive, although enough data are given for quite a clear picture to emerge. The studies cited fall into 3 groups:

Studies of smoking in Western populations: Studies 1-11 are cited in a recent paper by Higgins, Mahan and Wynder in Preventive Medicine (1988, 17, 116-128), 12 is the American Cancer Society million person study (Hammond, 1966, NCI Monograph 19, 127-204), 13 is the British Doctors Study (Doll and Peto, 1976, BMJ, 2, 1525-1536, and Doll and Peto, 1980, BMJ, 1, 967-971) and 14 is a large case-control study by Wynder and Kabat (Cancer, 1988, 62, 1223-1230). Study 14 is of particular interest as it

gives results for Kreyberg I (squamous, large cell, and oat cell) and Kreyberg II (adenocarcinoma, bronchiolar, and alveolar cell carcinoma) separately.

Studies of ETS in Western populations: Studies 15-22 are referenced in my recently circulated review of studies of passive smoking and mortality in adult never smokers (subsequently published as a book by Karger in 1992) and are all those Western lung cancer/ETS studies which present the relevant data in a suitable format.

Studies of ETS in Eastern populations: Studies 22-31 are also referenced in my review and correspond to 15-22 but for Eastern (Asian) populations.

2. Some relevant considerations

Before considering the data, 2 relevant points are worth making. Firstly, the percentage of lung cancers occurring among never smokers will depend strongly on 2 things - the frequency of ever smoking in the population, and the ever smoking/never smoking lung cancer relative risk. The relative risk itself will depend on how much and for how long the smokers have smoked. Table 1 illustrates the dependence of the lung cancer percentage on frequency of ever smoking and relative risk and shows large variation depending on the situation. Thus, for a population where 90% have ever smoked and where the relative risk is 10, only 1% of lung cancers will occur among never smokers. In contrast, for a population where only 25% have ever smoked and where the relative risk is

3, 50% of lung cancers will occur among never smokers.

Secondly, the formulae and subsequent tables are based on observed data and assume no misclassification of ever smokers as never smokers. Even quite a small misclassification rate can mean that a substantial proportion of lung cancer cases who are self-reported never smokers are actually ever smokers. This is particularly so when the relative risks and the frequency of ever smokers are high. Thus, suppose in truth 90% of the population have ever smoked and that the relative risk is 20, so that in fact only 0.55% of lung cancer cases occur among never smokers. If a random 1% of ever smokers deny smoking, what do we observe? Firstly, that only 89.1% of the population have ever smoked (not much difference from 90%). Secondly, that the relative risk drops from a true value of 20 to an observed value of 7.8 (a big reduction). Thirdly, that instead of only 0.55% of lung cancer cases occurring among never smokers we observe 1.55%, 64% of these being among true ever smokers. This illustrates the problem that if we design a study based on evidence in which misclassification occurs and then use more rigorous means to determine smoking habits, we may end up with materially less lung cancers than we had planned for.

3. Results

Table 2 shows results for males from 22 studies. In the 19 Western studies, an average of 2.4% of the lung cancers occur among never smokers. In the 3 Eastern studies, an average of 4.4%. The range of percentages is 0.5-7.3%. The average proportion of the populations who had reported ever having smoked is about 81% in both Eastern and Western studies, ranging from a high of around 95% for 2 old British and German

studies to a low of 64% for a modern Swedish study. As expected from Table 1, the study with the lowest frequency of ever smokers had the highest percentage of lung cancers occurring among never smokers. In the Wynder and Kabat study, it can be seen that the proportion of cancers occurring among never smokers is lower for Kreyberg I (1.7%) than for Kreyberg II (5.2%) consistent with the higher relative risks for lung cancers of the former type.

Table 3 shows results for females from 21 studies. There are very large differences between countries. There are 2 main groups.

The first is the 9 Eastern studies (bottom group) where an average of 24.5% report ever having smoked (range 13.0% - 40.8%), the percentage of lung cancers occurring among never smokers averaging 51.6% (range 34.4% - 75.9%). This is consistent with a relative risk averaging about 3 (see Table 1). The study with the lowest proportion of ever smokers has the highest proportion of lung cancers among never smokers (Inoue), and that with the highest has the lowest (Geng) as expected.

The second main group consists of the 9 Western studies 13-20 and 22. Here the proportion reporting ever having smoked, averaging 53.4% (range 40.7% - 60.5%) is much higher than for the Eastern females, though much lower than for the men. The proportion of lung cancers occurring among never smokers averages 13.2% (range 7.0% - 19.5%), consistent with a relative risk averaging almost 6 (see Table 1).

Three studies do not fit into this picture. The Trichopoulos results are clearly much more like a population of Eastern women than of Western women. The Lubin results, which are based on a number of countries, are in between the two main groups. The Hammond (million person) study has a relatively low percentage of smokers and a low

relative risk - consistent with it being an older study than the other Western ones.

It is again notable from the Wynder and Kabat study that the proportion of cancers among never smokers is substantially lower for Kreyberg I (6.0%) than for Kreyberg II (18.8%).

The proportion of all lung cancers (males and females combined) is also of some interest. Not all the results in Tables 2 and 3 can be combined as the sampling schemes in some studies differed by sex (and some studies provide data for one sex only). Table 4 shows results for some that can. The Western studies included average 4.2%; the Hirayama study has a higher proportion, 16.4%.

4. Summary

The tables show 3 typical situations, producing different percentages of lung cancers occurring among never smokers:

Men - where about 80% have smoked and where the percentage averages about 2 1/2%.

Western women- where about 50% have smoked and where the percentage averages about 13%.

Eastern women - where about 25% have smoked and where the percentage averages about 50%.

TABLE 1

Percentage of lung cancers occurring among never smokers in relation to frequency of ever smokers and relative risk in relation to smoking

	% Frequency of ever smokers (F)					
Relative risk (R)	10	25	50	75	90	95
1	90	75	50	25	10	5
3	75	50	25	10	4	2
5	64	37.5	17	6	2	1
10	47	23	9	3	1	0.5
20	31	13	5	2	0.6	0.3
50	15	6	2	0.7	0.3	0.1

Formula used : Percentage of lung cancers occurring among never smokers $= 100\ (100-F)/(RF+(100-F))$

TABLE 2

Number of lung cancers (N), number (n) and percentage (%) occurring among never smokers, and proportion (p) of control population who had ever smoked - males

	Study authors	Year	Country	N	n	%	p
1	Wynder & Graham	1950	USA	605	8	1.3	85.4
2	Doll et al	1952	GB	1537	7	0.5	95.5
3	Sadowsky et al	1953	USA	477	18	3.8	86.8
4	Randig	1955	Germany	415	5	1.2	94.2
5	Gsell	1956	Switzerland	150	2	1.3	80.7
6	Lombard & Snegireff	1959	USA	500	8	1.6	89.0
7	Abelin & Gsell	1967	Switzerland	118	2	1.7	64.5
8	Wynder et al	1970	USA	284	9	3.2	79.0
9	Joly et al	1983	Cuba	607	12	2.0	80.3
10	Damber & Larson	1986	Sweden	579	42	7.3	63.6
11	Lubin et al	1984	USA/Europe	6920	190	2.8	80.6
12	Hammond	1966	USA	1159	49	4.2	78.2
13	Doll & Peto	1976	GB	441	7	1.6	83.0
14	Wynder & Kabat						
	All	1988	USA	2085	64	3.1	76.8
	Kreyberg I	1988	USA	1278	22	1.7	77.5
	Kreyberg II	1988	USA	807	42	5.2	75.6
15	Buffler et al	1984	USA	455	11	2.4	79.9
16	Correa et al	1983	USA	1057	8	0.8	83.2
17	Hole et al	1989	Scotland	125	3	2.4	83.1
18	Humble et al	1987	USA	366	8	2.2	74.4
19	Lee et al	1986	England	814	15	1.8	83.5
23	Akiba et al	1986	Japan	260	19	7.3	81.2
24	Chan & Fung	1982	Hong Kong	208	2	1.0	78.9
27	Hirayama	1984	Japan	1292	64	5.0	82.3

TABLE 3

Number of lung cancers (N), number (n) and percentage (%) occurring among never smokers, and proportion (p) of control population who had ever smoked - females

	Study authors	Year	Country	N	n	%	p
11	Lubin et al	1984	USA/Europe	772	288	37.3	32.0
12	Hämmond	1966	USA	183	102	55.7	32.0
13	Doll & Peto	1980	GB	27	4	14.8	50.0
14	Wynder & Kabat						
	All	1988	USA	1012	125	12.4	52.4
	Kreyberg I	1988	USA	513	31	6.0	52.7
	Kreyberg II	1988	USA	499	94	18.8	52.1
15	Buffler et al	1984	USA	453	41	9.1	58.7
16	Correa et al	1983	USA	315	22	7.0	58.4
17	Hole et al	1989	Scotland	31	6	19.4	55.8
18	Humble et al	1987	USA	243	20	8.2	40.7
19	Lee et al	1986	England	258	32	12.4	60.5
20	Svensson et al	1989	Sweden	210	34	16.2	45.3
21	Trichopoulos et al	1983	Greece	102	77	75.5	10.4
22	Wu et al	1985	USA	149	29	19.5	58.4
23	Akiba et al	1986	Japan	152	94	61.8	20.6
24	Chan & Fung	1982	Hong Kong	189	84	44.4	26.5
25	Goo et al	1988	China	482	246	51.0	25.7
26	Geng et al	1988	China	157	54	34.4	40.8
27	Hirayama	1984	Japan	321	200	62.3	15.9
28	Inoue & Hirayama	1988	Japan	29	22	75.9	13.0
29	Koo	1987	Hong Kong	198	86	43.4	31.7
30	Lam 1	1987	Hong Kong	130	60	46.2	22.2
31	Lam 2	1987	Hong Kong	441	199	45.1	24.0

TABLE 4

Number of lung cancers (N), number (n) and percentage (%) occurring among never smokers - sexes combined

Study authors	Year	Country	N	n male	n female	n combined	%
Lubin et al	1984	USA/Europe	7692	190	288	478	6.2
Doll & Peto	1976/80	GB	468	7	4	11	2.4
Wynder & Kabat	1988	USA	3097	64	125	189	6.1
Correa	1983	USA	1352	8	22	30	2.2
Hirayama	1984	Japan	1613	64	200	264	16.4