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癌症流行趋势和防控策略研究研讨会

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院士论坛



中国恶性肿瘤流行趋势及预防

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摘要:癌症已成为一个全球性公共健康问题,近三十年以来,癌症发病数以年均 3%–5% 的速度递增;3/4 新增病例发生在新兴工业国家及发展中国家,癌症已成为人类第一位死因,根据 2002 年 IACR 报告,目前世界发病率最高的是肺癌、乳腺癌和大肠癌;死亡率最高的是肺癌、胃癌和肝癌。

世界卫生组织提出为应对不断上升的癌症发病率的紧迫性,世界卫生组织会员国在日内瓦第五十八届世界卫生大会上批准了一项关于预防和控制癌症的决议。此项决议呼吁所有会员国制定国家癌症规划,其中包括加强预防措施、及早发现和筛查以及改进治疗和姑息治疗。此外国际抗癌联盟(UICC)和中国抗癌协会也分别发表世界癌症宣言,号召大家携起手来共同抗击癌症。

目前在我国肿瘤已经成为第一大死亡原因。我国改革开放以来,经济、社会、环境和生活方式发生了快速变化,人口结构快速向老龄化转变,在这一特定历史时期,中国癌谱呈现特征性变化。乳腺癌、结直肠癌、肺癌、膀胱癌和肝癌死亡率上升很快。

以天津市居民为研究对象,建立历时近 30 年,覆盖 400 万居民的人群肿瘤发病死亡监测系统,开展了恶性肿瘤流行趋势、病因分析及预防干预等综合研究。揭示我国城市经济转型期恶性肿瘤总体发病率快速升高的趋势。1981–2002 年男性粗发病率年均上升 1.95%;女性粗发病率年均上升 2.25%。同时,1981–2002 年,男性粗死亡率年均上升 0.62%,女性年均上升 0.76%。人口老龄化是肿瘤发病率升高的主导因素。天津市男性发病前五位恶性肿瘤分别为肺癌、胃癌、肝癌、大肠癌和食管癌;女性前五位肿瘤分别为肺癌、乳腺癌、大肠癌、胃癌和肝癌。提出我国常见癌谱兼具发达国家和发展中国家的双重特征。

2008 年,利用中央财政补助地方卫生专项资金,中国抗癌协会受卫生部疾控局委托在全国 30 个省(区、市)53 个县(区)选择项目点开展妇女乳腺癌筛查工作,截止至 2009 年 5 月,全国总筛查人数 466 871,经病理确诊良性肿瘤 3823 例,乳腺癌 287 例,其中 II A 期及以下的早期乳腺癌 90 例,占 31%。通过大规模的人群乳腺癌筛查发现,由筛查方式发现早期癌较非筛查方式提高 23.06%。早期发现乳腺癌,不仅治愈率高,而且可以做“保乳”手术,术后各种辅助治疗也可减少,不但可节省医疗费用,也可以提高患者的生活质量。

总之,恶性肿瘤流行趋势分析和预防模式的研究表明建立我国恶性肿瘤综合防治体系有重要意义,同时也为建立适合中国人群生理特点和社会经济发展水平的常见恶性肿瘤的三级预防模式提供了科学依据。

CANCER EPIDEMIOLOGY AND PREVENTION IN CHINA

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Abstract: Cancer has become a global burden for public health. During the latest 3 decades, cancer cases increased by 3–5% annually in the world, 3/4 of the new cases happened in developing countries. Cancer has become the first cause of death. As reported by IACR in the year 2002, the top three cancers for incidence rate was lung, breast and colorectal cancer, and the top three cancers for mortality rate was lung, stomach and liver.

In response to the urgency of the rising incidence of cancer, WHO member states have today approved a resolution on Cancer Prevention and Control at the 58th World Health Assembly in Geneva. In addition, UICC and CACA developed World Cancer Declaration to call to action from the global cancer community.

Cancer is the first cause of death in China. Economy, society, environment and lifestyle changed rapidly in China. Population are aging, and cancer spectrum was changed. The mortality of breast, colorectal, lung, bladder and liver cancer was increased rapidly. Tianjin cancer registry covered about four-million population in Tianjin urban area over the last 30 years. Study on cancer epidemiology, etiology and prevention suggested a rapidly increasing trend of cancer incidence rate in China. The crude incidence increased by 1.95% per year for male and 2.25% per year for female from 1981 to 2002. Meantime, the crude mortality increased by 0.62% per year for male and 0.76% per year for female. The main cause of this continuous rise in cancer incidence was the effects of population aging. The top 10 cancer incidence rank was lung, stomach, liver, colorectal and esophagus cancer for male and lung, breast, colorectal, stomach and liver for female. Cancer spectrum in Tianjin is changing to the cancer spectrum of developed countries while keeping some characteristic of developing countries.

Chinese national breast cancer screening project was started from the year of 2008. Working with Chinese Ministry of Health, CACA is leading and coordinating this large project among 530000 women in 30 provinces in China. Until May, 2009, 466871 women were screened while 287 breast cancers and 3823 benign tumors were detected, which included 90(31%) early stage cancers. Cancers in early stage detected by screening were increased by 23.06% compared with which detected by non-screening methods. Early detection of breast cancer is one of the best ways to save a woman's life and it can lead to greater likelihood of cure.

In short, the study on cancer epidemiology and prevention study has shown the significance of the establishment of comprehensive cancer prevention and control system in China, and provides a scientific basis for the establishment of three grade prevention model of the common malignant tumors, which is suitable for the Chinese physiological characteristics and socio-economic development.



近 50 年来中国临床肿瘤学的进展

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近百年来肿瘤发病率不断增高,在我国居民死亡原因中已经位居前列,在卫生工作中也占有越来越重要的地位。成为主要威胁人民健康的常见病。作者回顾了很多肿瘤学进展中具有里程碑意义的成果,都是基于对于肿瘤认识的提高。重要科学的进展推动了临床肿瘤学的进步。

回顾 中国临床肿瘤的开端是 1933 年在北平协和医院成立的肿瘤组。新中国成立初期,由于当时全国卫生状况,国家无力重视肿瘤的防治。直到建国 10 年以后我国才开始重视肿瘤问题,并启动了比较全面的规划、建设和研究。并于 1954 年成立了上海肿瘤医院,1958 年成立了卫生部下属的中国医学科学院肿瘤医院(当时称日坛医院,地位等于美国的 NCI)。此后各省市相继成立了肿瘤防治机构。有关临床肿瘤学的发展,历史上曾经有过两次重要的大讨论。

第一次讨论,是 50 年代末中国医学科学院肿瘤医院建院之初,在几位临床肿瘤学元老,吴桓兴教授(时任中国医学科学院肿瘤医院院长)、金显宅教授(时任中国医学科学院肿瘤医院顾问)和李冰教授(时任中国医学科学院肿瘤医院党委书记兼副院长)的领导下,对临床肿瘤学的方向进行了讨论,制定了以综合治疗为模式的发展方向。

随之,在 1959 年的第一届全国肿瘤学大会上,与会者就临床肿瘤学发展达成 4 项共识,即:预防为

主、中西医结合、基础研究与临床研究结合、综合治疗。

虽然在今天,综合应用现有手段诊断、防治肿瘤已经深入人心,为国内外学术界所接受,但是这在当时还是难能可贵和具有远见的。吴桓兴是一位放射肿瘤学家,金显宅和李冰则是外科肿瘤学家,但他们共同支持和创建了一个当时正在发展中的新兴学科——肿瘤内科学。可见,他们已经清楚地认识到内科治疗将成为肿瘤治疗中不可缺少的重要手段之一。

第二次讨论,是 20 世纪 70 年代,周恩来总理对肿瘤界做出了重要指示:肿瘤是多发病、常见病;应当深入调查摸清我国的发病情况,并采取预防措施;结合我国具体情况和实践经验编写我国自己的参考书;大力开展高发区研究等等。这些指示明确了我国肿瘤学前进的方向,也成为我们以后一段时间工作的重要指导原则。

成果 为了纪念建国 60 周年,我们曾总结我们临床肿瘤学的重要成果(中国新药杂志 2009; 18: 1695-1700)。虽然我们遭遇了十年浩劫这样的干扰,但还是取得一定成绩。其中比较重要的有:

1、肿瘤高发区的研究

回顾 50 年来我国临床肿瘤学的成就,高发区防治研究(包括食管癌、鼻咽癌、肝癌和肺癌等)所取得

的成果受到世界同行的瞩目。卫生部在 1973~1975 年组织了全国居民死亡回顾调查,明确了我国癌症死亡的分布,编写了著名的《中华人民共和国恶性肿瘤地图集》并先后启动了高发区的病因、早期发现早期诊断早期治疗(称为“三早”),预防干预和综合治疗的各项研究。这些工作都受到国际同行的广泛认可。

例如对河南省林县食管癌现场研究始于上世纪 50 年代,针对有 1700 万人口的食管癌高发地区展开大规模普查。在调查的基础上,卫生部又受到全世界同行的重视。从 80 年代中期经过多次论证我们和美国 NCI 达成了协议,在高发人群开展维生素加微量元素的双盲干预实验,结果在 1993 年发表在 JNCI: 治疗组食管癌、胃癌和白内障发病率明显下降,成为全球第一个阳性试验。

1974 年,中国医学科学院肿瘤医院孙宗棠与上海的汤钊猷等在江苏启东开展大规模肝癌筛查工作,并提出了“小肝癌”和“亚临床肝癌”等概念,很快得到国际上的关注。为此,美国国立癌症研究所(NCI)将 1979 年度金质奖章授予孙宗棠、汤钊猷和朱源荣 3 位医师,以表彰他们在肿瘤早期诊断、早期治疗方面作出的巨大贡献。

1975 年开始,我们在云南个旧锡矿展开了肺癌现场研究,并在之后每年派医疗队协助开展筛查和治疗。还曾组织国际会议,邀请多国专家协助解决了病因问题的争论。我本人也曾在 1981 年的美国临床肿瘤学会(ASCO)年会上介绍了云锡肺癌的情况,受到广泛关注。之后,美国 NCI 邀请云锡矿工肺癌研究人员赴美讲学交流,并达成一些合作项目。

2. 抗肿瘤新药的临床研究

因此,寻找有效的抗肿瘤药物和治疗方法受到广泛关注。当然,在改革开发之前,由于历史原因导致临床试验方法不规范,所得到的结果也同样存在问题。1985 年,我国政府颁布《药品法》并且制定了

《新药临床审评规范》,从而使药品的审评走向规范化道路。

近半个世纪以来,我国在相当长的年代主要是学习和引进国外抗肿瘤药物和方法。但在肿瘤内科治疗领域内,我们仍然有一定开创性的工作,改善临床实践。例如,大剂量化疗治疗绒毛膜上皮癌;N-甲酰溶肉瘤素治疗睾丸精原细胞癌;全反式维甲酸和砷剂在急性早幼粒白细胞治疗中的应用;榄香烯治疗癌性胸水;参一胶囊抑制肿瘤新生血管;重组人血管抑制素提高非小细胞肺癌化疗效果等等。这些研究项目大多曾经获得国际上的大奖和国家奖,有大多数已经进入诊疗规范。

近年来,我国进入临床试验的创新药物明显增多,我们有理由相信,在未来 10 年内,我国肿瘤内科学将有长足的发展,尽快赶上国际先进水平。

由我国学者发起组织的、在亚洲开展的多中心 III 期临床研究,IPASS 研究,在 2008 年的欧洲肿瘤内科学会(ESMO)上公布了最终结果,论文发表在《新英格兰医学杂志》(NEJM)上。这项纳入来自 87 个临床中心的 1217 例初治晚期非小细胞肺癌患者的研究,比较了吉非替尼与标准化疗(卡铂+紫杉醇)疗效。研究发现在亚洲的非吸烟肺腺癌患者中,吉非替尼作为一线治疗优于传统化疗;这一优势尤其体现在存在表皮生长因子受体(EGFR)基因突变的肺癌患者中。这项结果,进一步促进了分子靶向治疗在常见肿瘤中的应用,更是我国临床肿瘤学者对世界医学作出的重要贡献。

EACH 研究是另一项大型随机对照 III 期临床研究,有包括中国大陆、台湾和韩国等多中心参与。研究比较了在晚期肝癌患者中,FOLFOX4 与 DOX 的疗效。结果显示,FOLFOX4 方案耐受性良好,而且显著延长患者的总生存和无进展生存。这是第一次证明系统化疗可以有效改善晚期肝癌患者预后。

另外,旨在比较厄洛替尼与传统化疗一线治疗



EGFR 基因突变肺癌患者疗效的 OPTIMAL 研究,也在 2010 年 ESMO 年会上报告了结果。并进一步为 TKIs 在晚期非小细胞肺癌患者中的应用提供了有力的证据。今年,我们在世界肺癌大会(WCLC)上报道了我们自己研发的酪氨酸激酶抑制剂(TKI)埃克替尼受到了国际同行的关注。说明在表皮生长因子 TKI 中疗效和其他 TKIs 相当但不良反应较小,以及得到国家药政部门批转上市。

展望 应当看到,肿瘤内科治疗已经有了很多进展,相当多的常见肿瘤,如滋养细胞肿瘤、急性白血病、睾丸肿瘤等,已经可以通过内科治疗达到根治;另一些常见肿瘤,如乳腺癌、肺癌、大肠癌、胃癌和骨肉瘤等,内科治疗也都占有相当重要的地位。此外,我们在肿瘤治疗理念方面已经有了很多进步,例如多种方法和途径的综合治疗、加强预防术后播散特别是远处转移的内科辅助治疗研究、重视生存率和生活质量的提高等。

近 10 年来,不断有新的针对肿瘤受体、调控和生长关键基因的靶向药物问世,从分子、受体、信号传导等方面的研究把病因、预防和治疗很好地连贯起来。分子靶向治疗虽然在现阶段还不能完全替代

传统的手术和放化疗,但其重大意义在于可以使治疗更具靶向性,更好地实现治疗个体化。而根据肿瘤的分子靶点决定治疗方案的策略与我国传统医学理论中的“辩证论治”和“同病异治、异病同治”不谋而合。靶点的诊断必然会成为未来肿瘤诊断以及个体化治疗方案制定的必要步骤。对患者的靶点监测应该受到重视。


随着研究的不断进展,新药和新方法的不断涌现,人们有理由相信临床肿瘤内科的治疗地位会越来越重要。

我们以及开始思考什么是我国临床肿瘤学的特点?其中包括:中西医结合,辩证论治-提高预见性;同病异治、异病同治-实现有的放矢;循证医学、规范化、个体化;扶正祛邪-重视宿主情况、基础疾病、免疫和骨髓功能重建等;治未病-重视预防、重视防止复发;以人为本-重视生活质量和远期结果等等。

结论 正是由于最新基础科学研究的成果推动了临床肿瘤学进入诊疗个体化时代。而基于近年来很多常见肿瘤逐步被制服,从分子水平认识肿瘤和越来越多的靶向药物进入临床实践,近年来,多数人对控制肿瘤的前景放弃了悲观论,持乐观态度。

PRINCIPLES, PROSPECTS AND PROOF FOR EFFECTIVE CANCER PREVENTION STRATEGIES

David Hill
(Cancer Council Victoria, Australia)

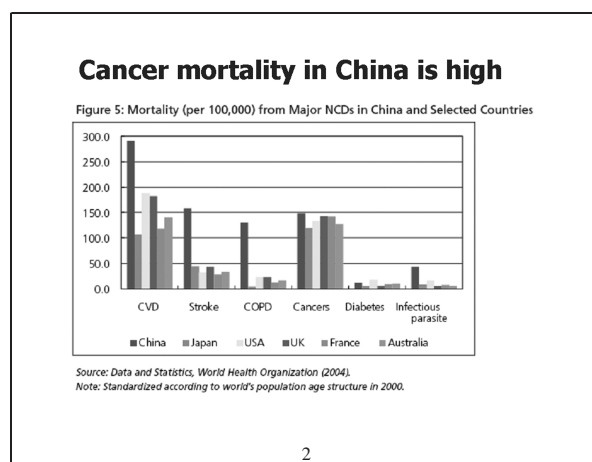
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Principles, prospects and proof for effective cancer prevention strategies

David Hill PhD, MD (hon)
Cancer Council Victoria, Australia
and
Immediate Past President, UICC
Tianjin, 21 September, 2011

www.uicc.org

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Public concern about cancer

Concern reflected in growth of civil society cancer organizations
Chinese Anti-Cancer Association
China 'spoke' of UICC

Need to convert citizen concern into 'whole of government' government action (that extends beyond health system)

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'Whole of government' action

'Upstream' causes of cancer a result of 'market failure'
Specialised bureaucracies like 'silos'
Characteristics of bureaucratic silos
Commercial interests and influence on government

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World Cancer Declaration (sign it at www.uicc.org/wcd)

1. Ensure effective delivery systems in all countries
2. Significantly improve measurement of the cancer burden
3. Decrease global tobacco, alcohol consumption and obesity
4. Ensure universal coverage of the HBV/HPV vaccine
5. Dispel damaging myths and misconceptions
6. More cancers diagnosed via screening and early detection
7. Improve access to diagnosis, treatment, rehabilitation and palliative care
8. Universal availability of effective pain control
9. Improve training opportunities for cancer control professionals
10. Reduce emigration of healthcare workers specialized in cancer
11. Major improvements in global cancer survival rates

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Percent cancer preventable by lifestyle changes and vaccinations*

| | High income countries | Worldwide |
|-----------------------------|-----------------------|-----------|
| Lifestyle | | |
| Smoking | 29% | 21% |
| Alcohol | 4% | 5% |
| Overweight/obesity | 3% | 2% |
| Physical inactivity | 2% | 2% |
| Diet: low fruit & vegetable | 3% | 5% |
| Sun exposure | 2% | 1% |
| Vaccines | | |
| HPV/Hepatitis B | Minor impact | 8-16% |

Based on Colditz and Biers 2010


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It is difficult to prove cancer prevention interventions "work" because:

1. Interventions need to be strong enough to reduce exposure to carcinogen
2. Carcinogenic process occurs over many years
3. Difficulty of sustaining behaviour change over a long time

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Cancer prevention opportunities: *environment and occupational exposures*

Asbestos, arsenic in drinking water, food contaminants (eg aflatoxins, pesticides) radiation

Indoor domestic air pollution (estimated 420,000 premature deaths in China)*

*Zhang et al Environmental Health Perspectives 2007 115:500-513

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Cancer prevention opportunities: *diet and dietary supplementation*

Work in progress!

Clear guidelines for action not available

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Cancer prevention opportunities: *medications*

Causation
Combined oestrogen plus progestin – breast

Prevention
Oral contraceptives –endometrium
Aspirin –colon *
Selective oestrogen receptor modulators - breast**
(eg Tamoxifen, Raloxifene)

*note negative cardiovascular and other effects
**reduction in breast cancer risk outweighs increased risk of uterine cancer

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Cancer prevention opportunities: *infection control*

Chronic infection due to-


- Helicobacter pylori (stomach, lymphoma)
- Human papilloma virus (cervix, mouth, pharynx)
- Hepatitis B, C (liver)
- Epstein-Barr virus (nasopharynx, Hodgkin, Burkitt)
- HIV (Kaposi, Non-Hodgkin lymphoma)
- Human herpes virus 8 (Kaposi, Non-Hodgkin lymphoma, schistosoma haematobium)

Proportion of cancer due to infections

- Developing world = 26%
- Developed world = 8%

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Cancer prevention opportunities: *behavioural risk factors (1)*


Smoking
Cancer of lung, mouth, oesophagus, larynx, bladder, pancreas, stomach, cervix, AML.

Alcohol
Cancer of mouth, pharynx, larynx, oesophagus, liver, breast, colon, rectum.

Physical inactivity
Colon ("convincing"),
post-menopausal breast, endometrium ("probable"),
lung, pancreas, pre-menopausal breast ("suggestive")

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Cancer prevention opportunities: *behavioural risk factors (2)*


Weight control
Oesophagus, colon, rectum,
endometrium, kidney, post-menopausal breast*

Sun exposure
Melanoma, basal and squamous carcinoma of skin

* Evidence of intervention effect on cancer rate Eliassen et al JAMA 2006 296:193-210


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Tobacco control: do we focus on prevention or cessation?

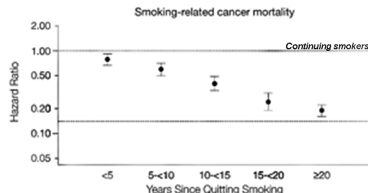
- Preventing uptake – 20+ year lag in impact on disease rates
- Cessation – disease impacts seen within 5 years
- Uptake rates dependent on adult smoking prevalence
- Therefore, cessation strategies essential

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Cancer risk begins falling within 5 years of quitting



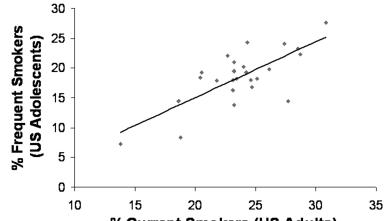
Nurses Health Study 1980-2004; Kenfield, S. A. et al. JAMA 2008;299:2037-2047.

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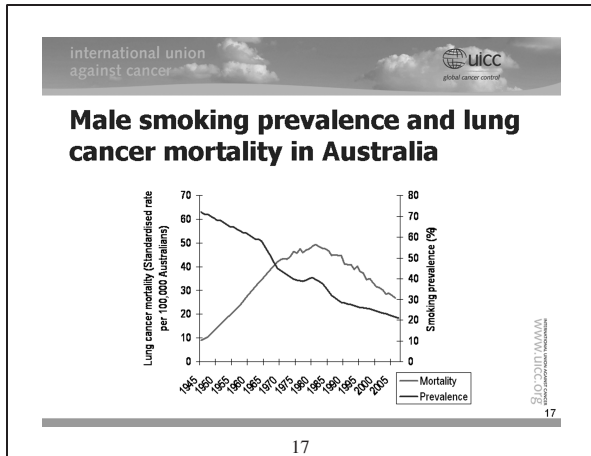
If more adults smoke, then more adolescents smoke




Each dot represents a state of the U.S.A.

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W.H.O. MPOWER Strategy for tobacco control

- Monitor tobacco use and prevention policies
- Protect people from tobacco smoke
- Offer help to quit tobacco use
- Warn about dangers of tobacco
- Enforce bans on tobacco advertising, promotion and sponsorship
- Raise taxes on tobacco

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Warning campaigns - principles

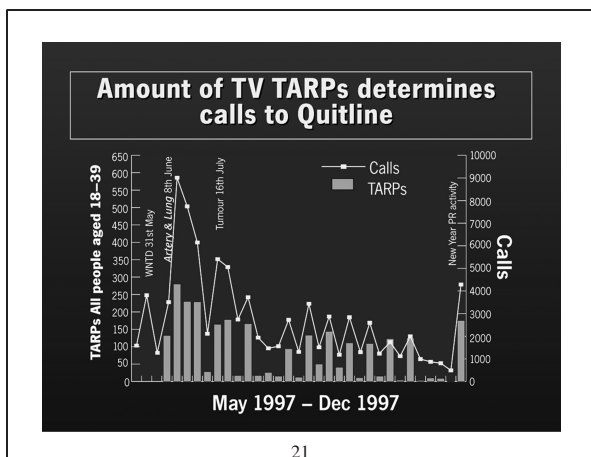
- Keep giving "new" news about health effects
- "Strong" messages about *health effects* (avoid humour, fun etc) and *testimonials* of people affected
- Get quitting smoking on "today's agenda"
- Use mass media (at optimal levels of intensity)
- Offer help and advice about quitting


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Rationale for 1997 Australian National Tobacco Campaign

See:
Hill D, Chapman S, Donovan R
The return of scare tactics
Tobacco Control 1998; 7: 5-8

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Smoking prevalence change replicated in 2 large population samples after campaign


| | Enumerated household sample % | Informant sample % |
|-----------|-------------------------------|--------------------|
| Benchmark | 23.5 | 23.7 |
| Follow-up | 22.1 | 22.0 |
| | p<.003 | p<.007 |

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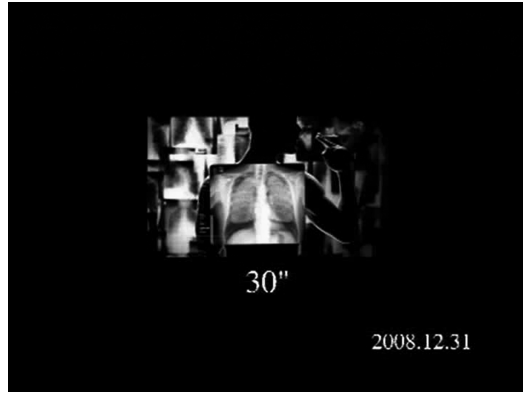
Mass media public education campaigns

- Controlled field experiments of media campaigns on youth (25 studies) and adult smoking (39 studies)
- Population-based evaluations of state/national mass media campaigns on youth and/or adult smoking (52 cross-sectional & 5 cohort studies)
- Mass media campaigns change youth attitudes about tobacco use, reduce smoking uptake and encourage adult cessation




US National Cancer Institute. 2012

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2008.12.31

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Controlling pro-tobacco marketing; principles

Since all forms of tobacco advertising promotion and marketing contribute to uptake and maintenance of smoking;

- Ban direct advertising
- Ban indirect advertising e.g. through sponsorship of events
- Neutralise attractive pack branding

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World first: Australia passes law to compelling plain tobacco packs

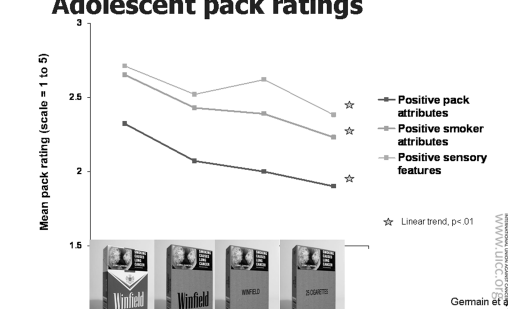


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Adolescent pack ratings



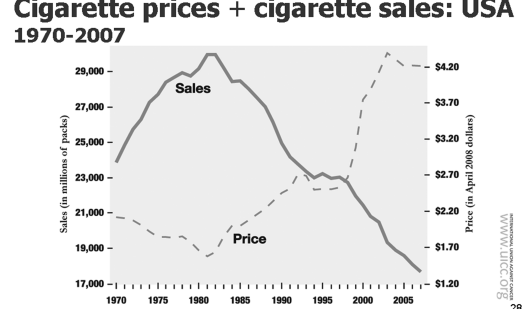
☆ Linear trend, p < 0.1

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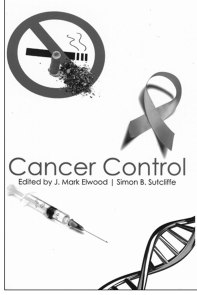
Cigarette prices + cigarette sales: USA 1970-2007



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Chapter 3
Achieving behavioural changes in individuals and populations
 David Hill, Helen Dixon

*In: Elwood JM, Sutcliffe SB (Eds).
 Cancer Control, Oxford: Oxford University Press, Chapter 3, 2010, pp 43-61*

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Big 5 principles of behaviour change (1)

Repeated and habitual behaviour is determined by extent to which a person:

- wants to do it,
- sees others doing it,
- has the capacity to do it,
- remembers to do it,
- is rewarded for doing it, or suffers for not doing it.

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Big 5 principles of behaviour change (2)

Repeated and habitual behaviour is determined by extent to which a person:

- wants to do it, *conscious motivation*
- sees others doing it, *modelling*
- has the capacity to do it, *resources, self-efficacy*
- remembers to do it, *memory and prompting*
- is rewarded for doing it, or suffers for not doing it, *reinforcement - positive or negative*

**Hill D, Dixon H, Achieving behavioural changes in individuals and populations; in 'Cancer Control' edited J. M. Elwood, S. B. Sutcliffe, Oxford Univ. Press, Oxford 2009.*


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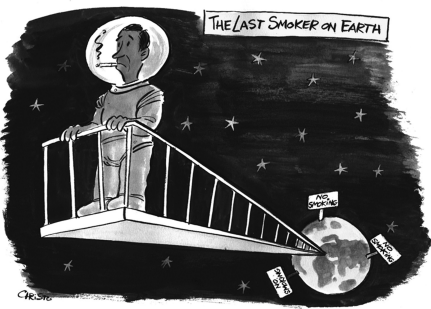
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Conclusions

Political 'will'
 Patient and public advocacy
 Knowledge already exists – it needs to be *applied widely*
 Tobacco: biggest priority and best evidence base
 Apply proven principles to change behaviour

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