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Health Risk and Financial Burden Due to Smokeless Tobacco (Khaini) Use in Bihar and Jharkhand Region of India- A Narrative Review

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Abstract

India is a global epicenter of oral cancer patients and the magnitude of the problem is continuously increasing in both male and female patients in various states. There is excess burden of oral malignancies in Bihar, Jharkhand and other eastern states and the risk factors associated with the disease are at its peak. Addressing the disease which is quite like an epidemic is a great challenge. Due to lack of education and financial facilities it creates a major public health issue and financial burden in these regions. This review paper discusses the ill effect of khaini, paan & gutkha, its risk to health and financial burden created by its habit in general living status.

Introduction

Oral Cancer is one of the top three types of malignancies reported in Indian subcontinent, as well as the sixth most predominant type of cancer worldwide, affecting both genders equally, although it is particularly common in men in developing countries [1]. In a recent study, it was reported that the incidence of oral cancer was 20 per 100,000 population and accounts for 30% of all cancer cases in our country [2]. According to the Global Adult Tobacco Survey of India conducted in 2016–2017, 28.6% (266.8 million) of all adults currently use tobacco, which is considered as the most common etiological agent [2]. In Bihar and Jharkhand, the consumption of smoking and smokeless tobacco is 25.9% and 38.9% respectively [3]. Out of all, 21.4% (199.4 million) use smokeless tobacco, which is a common oral abusive agent in lower socioeconomic groups [4].“Smokeless tobacco”(SLT) refers to the consumption of unburned tobacco, in the form of chewing, spitting, dipping, and snuff consumers ,chew the tobacco in the mouth [5].Due to lack of knowledge about the dangerous goods associated with the use of these substances, and they consume it for perceiving salutary goods, similar as mouth freshening, aid in digestion, origin- payoff, astringency, mood improvement, pressure relief, and oral cleaning [6]. SLT products are known to contain further than 30 carcinogens, including tobacco specific N- nitrosamines (TSNAs), nitrite, nitrate and heavy essence similar as nickel, cadmium and chromium. The carcinogens beget conformation of DNA adducts and posterior mutations in K- ras, p53 and other genes, leading to unbridled cell growth [7]. Other changes, including habitual original inflammation, oxidative stress and conformation of reactive oxygen species, may also contribute to tumor promotion [8]. Mechanisms similar as activation of Akt and protein kinase A lead to reduced apoptosis and increased angiogenesis and cellular metamorphosis.

In this the most important challenge is the lack of awareness and delay in diagnosis. Majority of cases are referred to tertiary health-care in a very advanced stage (Stages III & IV) which results in poor prognosis. Moreover, due to lack of adequate health care professionals and infrastructure in the rural area of the country leads to a delay in introduction of treatment. Surgery, Chemotherapy, and Radiotherapy are the three important pillars in the management of oral cancer. Surgery is considered as the most important out of the three, which is performed at the early stages of the disease. No doubt, surgery for oral cancer patients requires a team of dedicated professionals and a well-equipped centre with advanced diagnostic as well as postoperative management facilities. At present, surgical oncologists, head & neck oncologists, otorhinolaryngologists, oral and maxillofacial surgeons, and general surgeons are the specialists in its management. Apart from it, plastic surgeons are also involved in the

complex reconstruction of postsurgical defects. In addition to that, a team of anaesthetists, intensive care specialists, nursing staff, paramedical staff, nutritionists, and speech therapists are also important in intraoperative and postoperative care. All these facilities are possible only in hospitals like medical colleges and corporate sector health centres present in major cities of the country. A huge monetary burden is faced in managing this disease, which is another challenge both for the patients and for the health-care professionals which is leading to its poor prognosis.

Mechanism of Genotoxicity and Carcinogenicity

Paan, gutkha, and zarda are taken by mouth, chewed, sucked, or applied to the teeth and gums [9]. The World Health Organization has classified smokeless tobacco products as human carcinogenic compounds, in particular tobacco-specific nitrosamines, which account for 76 to 91% of the total N-nitroso compound (NOC) burden [10]. These products have been associated with oral and pancreatic cancers, cardiovascular disease, periodontal disease, asthma, and deformities in the women reproductive system [11]. Studies have shown that tobacco users who include slaked lime in betel quid or with areca nut experience carcinogenic and genotoxic effects in human oral epithelium cells which generate reactive oxygen species (ROS) in the oral cavity of chewers [12].

The different ingredients used in paan and gutkha have their own detrimental effects, such as catechu, which consists of tannin and polyphenols, which have a high tendency to cause esophageal cancer and are characterized by mutagenicity and clastogenicity [13, 14, 15]. The lime (calcium hydroxide) used can result in an alkaline pH, triggering ROS release and causing irritation of the oral mucosa and hyperplasia [16]. Areca nut consists of phenolic compounds, and tobacco releases various nitrosamines in the mouth that are responsible for proliferative abrasions and damage to DNA and fibroblasts (Fig.1). NOCs extracted from areca nuts, which contain the active substance 3- (methylnitrosamino) proprionitrile, have been found to cause genotoxicity and cytotoxicity responsible for tumors in the buccal cavity of smokeless tobacco consumers [17].The long-lasting and frequent presence of paan and gutkha in the mouth around the gums leads to inflammation of the oral mucosa, which causes the activation of T-cells and macrophages, and ultimately the release of prostaglandins which occurs in keratinocytes of the buccal cavity due to areca nut extract, and this plays a significant role in oral tissue fibrosis and cancer. Cytokines such as interferon-α, tumor necrosis factor (TNF), interleukin-6, and growth factor-like transforming growth factor-beta have been found to be produced at the sites of irritation which makes an important contribution to OSMF and premalignancy (Fig 2) [18, 19]. The nitrosamine in tobacco undergoes metabolic activation by cytochrome P450 enzymes, which may lead to the formation of N-nitrosonornicotine, a major carcinogen, which further leads to DNA damage and ultimately oral cance [20].

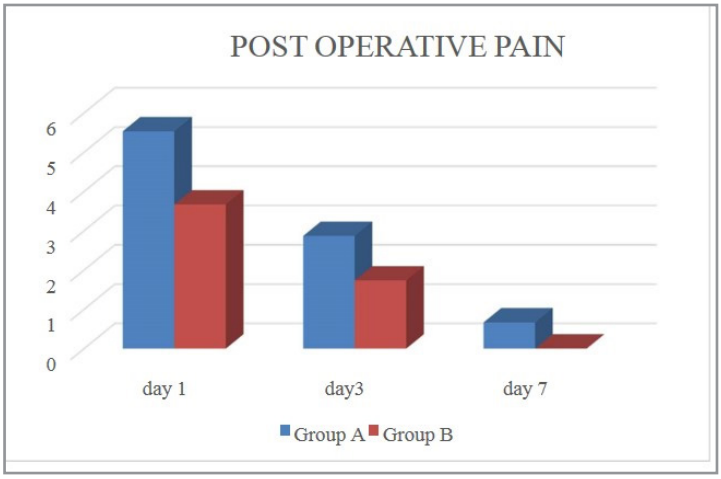

Figure 1: Roles of paan and gutkha in oral submucous fibrosis and Oral cancer, ROS (reactive oxygen species)

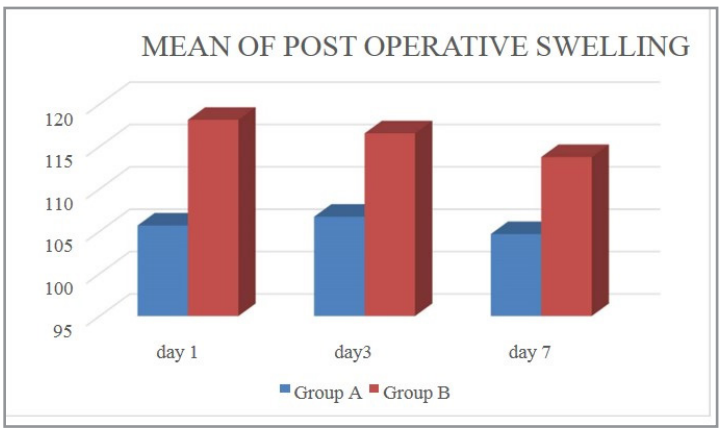

Figure 2: Initial events in the pathogenesis of mouth cancer. Interleukin 6, interferon Alpha, TNF, TGF beta.

Magnitude of Smokeless Tobacco Consumption and its Relation to Cancer Illness in Bihar & Jharkhand Region

Tobacco has been the most significant modifiable risk factor for oral cancer. 80-90% of oral cancer cases is directly linked to the use of tobacco. Greater than 80% of the total tobacco users in the world reside in low and middle-income countries. According to National Family and Health Survey, about one in ten adults aged 15 to 49 years use some form of tobacco in India [21]. The use of tobacco is higher among males and more common in uneducated, backward and economically weak sections of the society. There is inter-state variation in the prevalence and use of different forms of tobacco in India. The north-eastern states have the highest prevalence of tobacco use in India with Tripura at the top as per the report of the 2016-17 Global Adult Tobacco Survey (GATS-2). In Bihar and Jharkhand, the consumption of smoking and smokeless tobacco is 25.9% and 38.9% respectively as given in Figure 3 [22]. The state of Jharkhand has shown higher use of tobacco than the national average, with approximately 38.9% of the adult population who are 15 years or above using tobacco in any form [23]. Of these, 59.7% males, 17% are females, while smokeless tobacco use is 27.7%, smoking 3.5% and dual use is 7.7% [23].

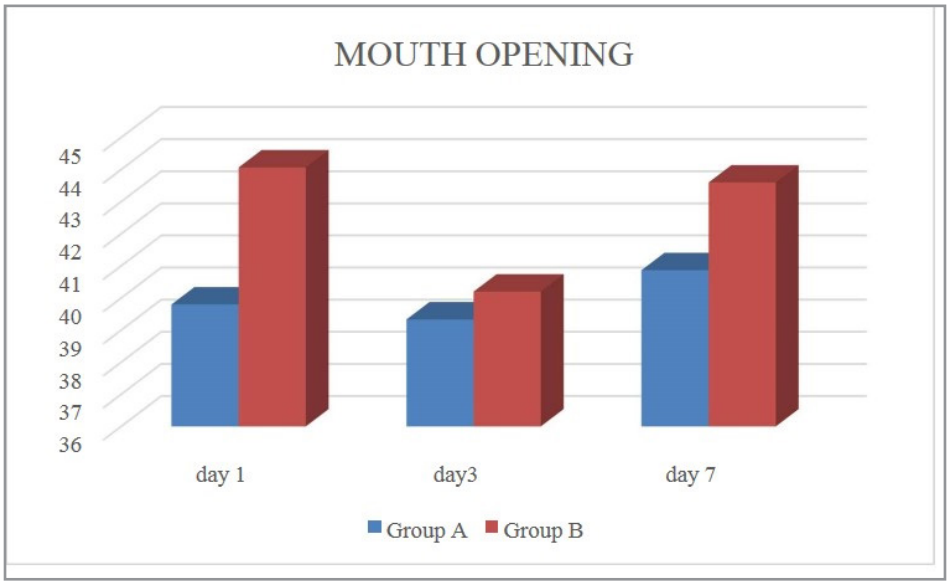

Figure 3: Prevalence of tobacco use (both smoking and smokeless) among states and UT in India, GATS-2.

The government of India recently released the key findings from Phase 1 of the National Family Health Survey conducted in 2019–20, which also included information regarding current tobacco use among Indian adults in 22 states and union territories [24]. The results are compared with those of the GATS-3 to track the progress in these Indian states (Table 1). Further, the results are stratified in terms of gender and place of residence (rural vs urban) to assess the heterogeneity of tobacco use among Indian adults [24]. The prevalence of tobacco use among men has declined in most states, except Sikkim, Goa, Bihar, Gujarat, Himachal Pradesh, and Mizoram, where an upward trend can be seen [24]. In the case of women, the prevalence has declined in almost all states except Mizoram and Sikkim [24]. Tobacco use in north eastern states remains a challenge5, where prevalence is still quite high [24]. The prevalence of tobacco use in rural areas is higher than in urban areas [24]. The absolute number of tobacco users in India is still very high due to its huge population, which has a high risk for developing various chronic diseases [24]. Despite all cessation policies, people are still consuming tobacco in both forms in India24. The tobacco users should be strongly encouraged to quit tobacco to eliminate long term detrimental effects on their health [24]. The decline in tobacco use definitely shows some positive signs for tobacco prevention and cessation programs in India, but it is yet far from achieving the goal of a tobacco-free India [24].

Table 1: Prevalence (%) of tobacco use among men and women aged ≥15 years across the states of India

State	NFHS-5 (2019-20)		GATS (2016-17)	
	Men	Women	Men	Women
Andhra Pradesh	22.6	3.8	30	10.1
Andaman and Nicobar Islands	58.7	31.3	NA	NA
Assam	51.8	22.1	62.9	32.9
Bihar	48.8	5	43.4	6.9
Dadra and Nagar Haveli, Daman and Diu	38.6	2.9	NA	NA
Goa	18.2	2.6	15.3	4
Gujarat	41.1	8.7	35.5	10.4

Himachal Pradesh	32.3	1.7	30.4	1.7
Jammu and Kashmir	38.3	3.6	39.7	6.2
Karnataka	27.1	8.5	35.2	10.3
Kerala	16.9	2.2	23	3.6
Ladakh	35.7	3.2	NA	NA
Lakshadweep	28.5	17.5	NA	NA
Maharashtra	33.8	10.9	35.5	17.1
Manipur	58.1	43.1	62.5	47.8
Meghalaya	57.7	28.2	59.8	34.2
Mizoram	72.9	61.6	64.9	52.4
Nagaland	48.4	13.7	54.2	31.7
Sikkim	41.3	11.7	26.4	8.4
Telangana	22.3	5.6	25.9	9.8
Tripura	56.9	50.4	67.5	61.4
West Bengal	48.1	10.8	48.5	17.9

In terms of exposure, consumption of SLT was described in terms of duration (number of months/years of consumption) and frequency (number of times of consumption per day) [25]. Among 50 SLT users (exposed), 29 subjects consumed khaini whereas 21 consumed gutkha [25]. When duration of the habit was being compared, the majority of the subjects (24 SLT users) were reported with >10 years, followed by <5 years (15 SLT users) and 5-10 years (11 SLT users) [25]. The mean average of duration of khaini consumption was 16.14 years at a frequency of 11 times / day [25]. The mean average duration of gutkha consumption was 6.24 years at a frequency of 6 times/day [25]. Various oral mucosal changes observed were white lesions (16 SLT users), proliferative/ulcerative growth (17 SLT users), and mixed red and white lesions (2 SLT users). No mucosal changes were observed in 15 SLT users and all the 50 nonusers.

Table 2. shows the distribution of oral mucosal changes seen in SLT users according to duration of consumption. Burning sensation was noted in 26 SLT users [25].

Table 2: Distribution of oral mucosal changes seen in SLT users according to duration of consumption

riable	No mucosal changes	White lesions	Mixed red and white lesions	Proliferative/ulcerative growth	Total
<5 years	8	4	1	2	15
5-10 years	6	5	0	0	11
>10 years	1	7	1	15	24

Treatment Plan

Treatment for advanced oral cavity squamous cell carcinoma (OCSCC) requires multi-modality therapy. Surgical resection is the preferred initial treatment modality, because high-dose radiation to the mandible can result in the development of osteoradionecrosis [26]. During the removal of disease in the oral cavity, an attempt is made to achieve a 1-1.5cm soft tissue margin around gross tumor. When the mandible is involved, marginal mandibulectomy is acceptable if the outer table of cortical bone is not directly invaded by tumor, while segmental resection of the mandible is preferred if there is gross bone invasion. When local disease is advanced, a more complex resection and reconstruction is often required for least functional and cosmetic defects [27].

Lymph node metastasis is common in OCSCC, occurring in roughly 45% of patients at presentation [28]. Neck dissection, the en bloc resection of cervical lymph nodes, has long been advocated for the removal and control of metastatic disease in the cervical region [29, 30]. When extensive disease is present, and removal of the sternocleidomastoid muscle is necessary, either regional or free-tissue transfer is often performed [31, 32, 33]. In the current strategy for oral cavity cancer, the literature supports that modified radical neck dissection, where all five levels of lymphatic tissue are removed, is reserved for cases where there is extensive disease, such as the presence of N3 disease, extensive extracapsular spread, or when there is identifiable disease in levels IV or V.

A variety of reconstruction options exist for oral cavity defects after surgical resection, and methods of reconstruction range from healing from secondary intention or primary closure, to reconstruction with skin grafts, local or regional flaps, to microvascular reconstruction with free-tissue transfer. The radial forearm free flap & anterolateral thigh flap are the primary reconstruction options for large partial glossectomy defects and are

associated with improved deglutition and speech [34-38]. Total glossectomy defects offer additional challenges and is a particularly morbid procedure, and the aspiration risk associated with resection of the base of tongue. Reconstruction of the total glossectomy deficit requires significant tissue bulk for replacement, and this is most often accomplished with the rectus abdominus or lattisimus dorsi free flap [39, 40].

Primary microvascular flap & osteocutaneous flaps have been described for the potential reconstruction of the bony and soft tissue defects after composite resection of cancer involving the mandible. These include the fibular free flap, radial forearm osteocutaneous, scapula osteofasciocutaneous, and iliac crest osteomyocutaneous flaps [38]. All these reconstructions have greatly increased the ability of the head and neck surgeon to resect advanced local disease with adequate restoration of speech, deglutition, oral competence, and cosmesis.

For patients with advanced local disease, or for those with multiple or extensive lymph node involvement, post-operative radiotherapy (PORT) has become the standard of care. Retrospective data has shown that PORT improves local-regional control and survival in these patients. PORT has become widely used for patients with stage III or IV OCSCC [41, 42, 43]. Perineural invasion, oral cavity disease site, positive surgical margins, multiple positive lymph nodes & extracapsular spread of lymphatic disease have been identified as unfavourable factors. During the last decade, studies have evaluated the utility of triple modality therapy, adding concurrent cisplatin to postoperative radiotherapy [44]. In 2004, two landmark randomized multi-institutional studies, RTOG 9501 and EORTC 22931, demonstrated the advantages of the addition of platinum-based chemotherapy to postoperative radiation in patients with high-risk, resectable head and neck squamous cell carcinoma. Both studies showed improvement in local-regional control and disease-free survival with concurrent cisplatin-PORT, and the EORTC study reported an improvement in overall survival [45, 46].

Financial Burden

Global Burden of Disease (GBD) suggest that about 70 percent of all cancer deaths are now concentrated among low and middle-income families [47]. The medical expenditure mainly includes information on doctor's/surgeon's fee, expenditure on medicines, diagnostic tests, bed charges and other miscellaneous expenses (like attendant charges, physiotherapy charges, personal medical appliances, blood and oxygen) [48]. The average out of pocket (OOP) spending on inpatient care in private facilities is about three-times that of public facilities, that is Rs 84,320 and Rs 29,066 respectively. Furthermore, treatment for about 40 percent of cancer hospitalization cases is financed mainly through borrowings, sale of assets and contributions from friends and relatives which is known as distressed financing. This high reliance on OOP spending is a major concern and hence it can potentially jeopardize the customary living standards of the households in Bihar and Jharkhand.

Discussion

Oral cancer is one of the commonest cancers in India. Being one of the prime causes, tobacco is still consumed in both chewing and smoking form in India. Most of the subjects belonged to lower socioeconomic scale. The low socioeconomic state maybe a risk factor for poor oral hygiene which further increases the risk of oral cancer in tobacco chewers. Majority of cases starts with the lesions of buccal cavity, tongue, floor of the mouth and the gums are affected by precancerous lesions which lead to oral cancer later. Dose and duration of tobacco consumption is well established risk factor for oral cancer. Several studies from India in the past have shown that the tongue is the most common site involved in the malignant process. However, the other common site of cancer is buccal mucosa particularly the left side.

Tobacco is the number one enemy of quality and quantity of human life in the developing countries due to its multidimensional effect. Wide awareness of its adverse effect is not enough to bring its popularity down. On the one hand, it attracts the adolescents as a fancy practice and on the other, its addictive property makes for a person almost impossible to quit it once addicted. This is the reason why the success of anti-tobacco programmes is not seen in spite of wide-spread efforts nationally and internationally. It is potentially associated with several types of cancers such as cancer of lung, larynx, oral cavity, esophagus, urinary bladder, stomach, pancreas, cervix and more recently of haematopoietic system (USDHHS, 1989). Tobacco is also significantly associated with many other major health problems like coronary artery disease, obstructive airway disease, peripheral vascular disease and pregnancy complications (including intra-uterine growth, retardation and variety of neoplasms) [49].

Men in the age group of 15−49 years are more prone to tobacco use than women in the same age group. An estimated 57 per cent of men and 11 per cent of women used some form of tobacco (IIPS, 2007), resulting in more estimated incidences of cancer in males than females in the period2015−25 [49]. Tobacco chewing is more prevalent than smoking in many areas (Reddy & Gupta, 2004) [50]. Another study conducted by Prasad and Dhar (2017) shows higher number of tobacco users in males [51]. Some of the studies indicate that one-third of reported cancers are oral cancers and 90 per cent of oral cancer patients are tobacco users (Gupta, 1999; Shimkhada& Peabody, 2003) [52, 53].

Pallawee Choudhary et al stated that knowledge regarding the screening of oral cancer was low in the study population [54]. This was in accordance to the results of the study conducted on Ayurveda and Homeopathy practitioners in Davangere and another study which was conducted on medical practitioners [55, 56]. The relatively less awareness pertaining to risk factors and clinical assessment techniques was also reported in primary care clinicians in England [57]. In their study, 30% doctors disagreed when enquired about self-sufficiency regarding knowledge of oral cancer. Fotedar V, etal [58]. also reported 66.6% medical students disagreed/strongly disagreed that their knowledge concerning the prevention and recognition of oral cancer is adequate. Lack of confidence about treating oral cancer was observed in doctors of Davangere district as well [55].

Ali et al stated that, the majority of patients of oral cancer were from poor economic manual workers (78%). Poor people used to consume more tobacco products because of less education and false beliefs [59]. They have also founded that duration of tobacco consumption is also a significant risk factor in causation of oral cancer. Tobacco exposure in 35% of patient was formore than 20 years where as in 25 % of patient tobacco exposure was

of 10-20 years. Oral cancer occurs preferentially in tongue, buccal mucosa and gingiva, exhibiting predilection for men over 50 years old.

Diagnostic infrastructure in many parts of India is scarce. The services of a pathologist or pathology/cytology centre which are crucial for diagnosing cancer are not available in many districts in India. There is a significant urban concentration of facilities because of economic and geographic constraints and lack of man power. A significant number of cancers diagnosed in the population are not treated. Lack of uniform protocols for management, the affordability and availability of cancer treatment shows broad disparities.

In India, oral cancer is detected mostly at advanced stages when the prognosis becomes poor and people are left with no choice for treatment. However, if they can be screened and diagnosed at an early stage, it would ensure improved treatment outcome, better curing rates and will also bring down the treatment cost so that it can be affordable and at the same time will drastically reduce the morbidity rate. In country like India, cost-effective oral cancer screening must be carried out by trained clinicians, health care professionals and dental surgeons in large and high-risk population (people using tobacco, alcohol, areca nut or with poor oral hygiene) as opportunistic screenings or population-wide screenings. Studies have proved that early detection and screening of oral cancer can significantly reduce the mortality due to the disease.

Conclusion

Tobacco smoke contain multiple carcinogens enough to induce process of carcinogenesis in oral cavity. People of lower socio-economic status mainly consumes khaini & gutka which increases the financial burden after the disease. Management of cancerous lesion costs multiple times of their monthly income, which in the end jeopardize their family living status. Smokeless tobacco specially in our country in the form of paan, khaini, gutka are heavily consumed from the young age. So, it has to stop at any cost to decrease the incidence of oral cancer and improve their livelihood.

Contribution Details (To be Ticked Marked as Applicable)

Contribution	Contribution Nmae
Concept, Design, Definition of intellectual content, Data acquisition, manuscript review	Dr Anshuman Kumar
Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review and Guarantor	Dr Birsubhra Roy- Guarantor

Summary of Work Done by the Contributors

The Concept and design of the following review article was put forward by Dr Anshuman Kumar. After that, literature search, Clinical studies, Experimental studies, Manuscript preparation, Manuscript editing, Manuscript review was done by Dr Birsubhra Roy.

Conflicting Interest (If Present, Give More Details)

No conflict of interest to disclose

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Availability of Data and Materials

Not applicable

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